

EXHIBIT

7

Lembke Report

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EXPERT REPORT, ANNA LEMBKE, M.D.

April 15, 2024

RELATING TO

Tarrant County, v. Purdue Pharma, L.P., et al. Case No. 1:17-md-2804

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literature searches of research on the subjects of addiction and pain treatment, which is essential to my work with my patients. Indeed, given the large and increasing role of opioid drugs in addiction, the fields of addiction and pain medicine are inevitably intertwined, such that it is essential to my practice to remain aware of the state of scientific inquiry in both fields. Specifically for this Report, I have considered the materials listed in Exhibit B, attached. I hold the opinions stated in this Report to a reasonable degree of scientific certainty.

35. Attached as Exhibit A is a copy of my current curriculum vitae and a list of all publications authored by me in the past 10 years.

36. Attached as Exhibit B is a list of data or other information considered by me in forming the opinions expressed herein.

37. Attached as Exhibit C is a statement of my compensation for services performed in this case.

38. Attached as Exhibit D is a list of all cases in which I have testified as an expert at trial or by deposition during the past four years.

B. Opinions

For the reasons set forth in detail in this Report, I hold the following opinions:

1. The addictive nature of medicinal opioids has been known for centuries. The Pharmaceutical Opioid Industry's misrepresentations of the safety and efficacy of prescription opioids reversed a century of appropriate restrictions on the use of these dangerous drugs, and substantially contributed to the current opioid epidemic.

2. Addiction is a chronic, relapsing and remitting disease with a behavioral component, characterized by neuroadaptive brain changes resulting from exposure to addictive drugs. Every human being has the potential to become addicted. Some are more vulnerable than others. Risks for becoming addicted include genetic, developmental, and environmental factors (nature, nurture, and neighborhood). One of the biggest risk factors for addiction is simple access to addictive drugs. When supply of an addictive drug is increased, more people become addicted to and suffer the harms of that drug. Prescription opioids are as addictive as heroin, and the Defendants' conduct in promoting increased supply and widespread access to prescription opioids has resulted in an epidemic of opioid addiction and overdose death.

3. Opioid prescribing began to increase in the 1980s and became prolific in the 1990s and the early part of the 21st century, representing a radical paradigm shift in the treatment of pain and creating more access to opioids across the United States.

4. The Pharmaceutical Opioid Industry contributed substantially to the paradigm shift in opioid prescribing through misleading messaging about the safety and efficacy of prescription opioids. The Industry disseminated these misleading messages through an aggressive sales force, key opinion leaders, medical school curricula, continuing medical education courses, clinical decision support tools, professional

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medical societies, patient advocacy groups, the Federation of State Medical Boards, and The Joint Commission.

5. Opioid distributors collaborated with opioid manufacturers and pharmacies to promote sales of opioid pain pills. Such coordinated efforts included programs to give away free samples of opioids, coupons to discount opioids, and promotion of specific opioid products under the guise of education. These activities increased the population of opioid users, dose and duration of opioid use, and the risk of opioid misuse, addiction, dependence, and death.

6. Pharmacies leveraged their unique and pivotal position in the opioid supply chain to contribute to the unprecedented and unchecked flow of opioid pain pills into the community. They alone had direct contact with opioid manufacturers and distributors upstream, and patients and prescribers downstream. Their coordinated efforts included direct mailings and media campaigns, continuing medical education courses for pharmacists, partnering with pro-opioid industry advocacy and lobbying organization, and creating stores where prescription opioids were readily available and abundant, sometimes called “Super Stores.” They ignored ‘red flags’ for misuse and diversion (including concerns expressed by their own pharmacists), and failed to provide pharmacists with sufficient time, resources, or incentives to investigate red flags. They also failed to use or analyze their own dispensing data to assist pharmacies in identifying red flags. By increasing and assuring the supply of opioids, and failing to provide effective controls against diversion, pharmacies contributed to opioid misuse, addiction, dependence, and death.

7. No reliable scientific evidence shows that long-term opioid therapy is effective for chronic non-cancer pain.

8. The Pharmaceutical Opioid Industry misrepresented that the risk of addiction to prescription opioids is “rare,” or “less than 1%,” when in fact prescription opioids are as addictive as heroin, and the risk of addiction is far higher than stated by the Industry. The best, conservative data show an opioid addiction prevalence of 10-30% among chronic pain patients prescribed opioids.

9. Increased supply of prescription opioids contributed substantially to more individuals becoming addicted to opioids and transitioning from prescription opioids to illicit sources of opioids such as heroin and fentanyl (The Gateway Effect).

10. Increased supply of prescription opioids contributed substantially to more individuals, including newborns, becoming dependent on opioids, increasing their risk for opioid-related morbidity and mortality (The Dependence Effect).

11. Increased supply of prescription opioids contributed substantially to diversion of prescription opioids to individuals for whom they had not been prescribed (The Tsunami Effect).

12. The increased supply of prescription opioids through licit and illicit sources resulted in a prescription opioid epidemic in the United States. “Epidemic,” defined as an

outbreak of disease that spreads quickly and affects many individuals at the same time, is the appropriate term to describe the increase in opioid related morbidity and mortality beginning in the 1990s and continuing to the present day.

13. There is no doubt a cause-and-effect relationship exists between the oversupply of prescription opioids and the opioid epidemic.

14. For the reasons explained, the Pharmaceutical Opioid Industry bears responsibility for the misrepresentation of safety and efficacy, the ubiquitous distribution of prescription opioids, and the unchecked dispensing of prescription opioids, which resulted in the ongoing epidemic. To the extent that other factors contributed, those conditions were exploited by the Industry to increase the extent of harm.

15. Ending the epidemic of opioid addiction, dependence, and death will require significant investment of resources. An effective strategy will be multifaceted and will accomplish the following: prevent new cases of addiction, dependence, and death (primary prevention), limit progression of harm (secondary prevention), and treat existing cases (treatment). These changes will require curbing opioid prescribing, re-educating patients and health care providers, creating de-prescribing clinics, promoting naloxone and other harm-reduction strategies, and building an enduring medical infrastructure to treat addiction.

C. Detailed Statement of Opinions

1. The addictive nature of medicinal opioids has been known for centuries. The Pharmaceutical Opioid Industry's misrepresentations of the safety and efficacy of prescription opioids reversed a century of appropriate restrictions on the use of these dangerous drugs, and substantially contributed to the current opioid epidemic.

- a. Opioids are among the world's oldest known drugs. Use of opium from the poppy plant for medical, recreational, and religious purposes can be traced throughout history and across continents, beginning in the 4th century B.C.²⁸
- b. In the 19th century, two major scientific advances in medicinal opioids had far-reaching consequences. In 1804, German pharmacist Friedrich Serturmer isolated morphine, an opioid alkaloid derived from opium and ten times as potent.²⁹ In 1855, Alexander Wood invented the hypodermic syringe, making possible fast easy administration of morphine.³⁰

²⁸ Lembke A. Psychology of Addiction and Recovery. Lecture: History of Addiction (Stanford University, Fall/Winter 2020)

²⁹ Meldrum ML. A capsule history of pain management. *JAMA*. 2003;290:2470-2475, at p. 2471

³⁰ Lembke, "Drug Dealer, MD", fn 3, above, at p. 42. See also Meldrum, "Capsule history", fn. 29, above, at p. 2471.

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- c. It was assumed (wrongly) that opioids administered by a doctor using a hypodermic syringe would not be addictive. During the Civil War, opium, laudanum, and hypodermic morphine were used extensively to treat soldiers and Victorian housewives alike. Hypodermic morphine soon became the major driver of America's first opioid epidemic. Hundreds of reports in late nineteenth century medical journals detailed iatrogenic (physician-initiated) cases of morphine addiction. The risk of addiction increased in cases where doctors continued to administer hypodermic morphine over long periods of time for protracted illnesses.³¹ The two most important risk factors were exposure to opioids and a history of chronic illness. In the 1870s and 1880s, America's per capita consumption of opioids tripled.³²
- d. In 1897, Bayer chemists, trying to find a less addictive form of morphine, synthesized heroin. Heroin was marketed by Bayer as a cough and cold remedy alongside Bayer Aspirin from 1898 to 1910.³³
- e. The opioid addiction epidemic of the late 19th and early 20th century (Narcomania) led to ever-stricter laws and regulations regarding the prescribing and dispensing of opioids in medical practice, beginning in the early 1900s with the Harrison Narcotic Act, which effectively made heroin illegal.³⁴
- f. As a result, the first several decades of the 1900s saw a steady decrease in the per capita consumption of medicinal opioids.³⁵
- g. Subsequent opioid epidemics in the 1940s and 1970s were smaller scale heroin epidemics unrelated to medical prescribing.³⁶ They were targeted and quelled through a process of repatriating Vietnam War veterans, criminalization, and methadone maintenance treatment.³⁷
- h. In 1970 the Controlled Substances Act (CSA) was passed, which serves as the cornerstone of today's drug scheduling system.³⁸ Schedule I drugs were prohibited. Schedule II drugs, including medicinal opioids, were tightly regulated with dire warnings of addictive potential, no prescription refills, triplicate order forms for transfers, production quotas, enhanced storage

³¹ Courtwright DT. "Dark Paradise: A History of Opiate Addiction in America". Harvard University Press; 2001, at pp. 46-47.

³² *Id.* at pp. 2-3 and 62-63.

³³ Lembke, "Drug Dealer, MD", fn. 3, above, at pp. 30-31

³⁴ *Id.* at footnote p. 57.

³⁵ Courtwright, "Dark Paradise", fn. 31, above, at p. 29

³⁶ *Id.* at p. 8.

³⁷ *Id.* at p. xii.

³⁸ Lembke, "Drug, Dealer MD", fn. 3, above, at pp. 57, 31 and 5.

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security requirements, and preapproval for all imports and exports.³⁹ Drugs included in Schedules III-V were considered to have lower potential for abuse.

- i. Medical training and education throughout the 20th century, save for the last two-plus decades, was filled with warnings about the addictive potential of medicinal opioids, even when prescribed to patients with severe pain and dire illness, but especially when used long term in the treatment of chronic pain. Physicians were urged to use opioids sparingly, for short duration, and only in cases of severe trauma and at the end of life.⁴⁰ For example, a peer-reviewed study published in 1954 concluded “Morphine is not the answer to chronic pain. Because of the development of tolerance to the analgesic effects of morphine, alleviation of pain becomes inadequate. Under such circumstances the physician, by gradually withdrawing narcotics, does not deprive the patient of any actual benefit but protects him and his family from the possible legal, social, or economic difficulties attendant on opiate addiction. The administration of morphine to a patient with chronic pain is a short-lived type of kindness. Long-term kindness would begin when opiates are withheld or withdrawn in favor of other therapeutic measures.”⁴¹
- j. The current opioid epidemic in the United States, occurring almost exactly 100 years after the first major opioid epidemic, was ushered in by the reversal of a century of prudential legislation and medical training. The result, since the 1990s, has been a prolonged period of opioid overprescribing with concomitant opioid addiction, dependence, and overdose death. When Defendants claim that knowledge of the addictive potential of medicinal opioids is new, they ignore 100 years of medical experience, knowledge, and legislation.⁴² The addictive nature of medicinal opioids has been known for centuries.

2. Addiction is a chronic, relapsing and remitting disease with a behavioral component, characterized by neuroadaptive brain changes resulting from exposure to addictive drugs. Every human being has the potential to become addicted. Some are more vulnerable than others. Risks for becoming addicted include genetic, developmental, and environmental factors (nature, nurture, and neighborhood). One of the biggest risk factors for addiction is simple access to addictive drugs. When supply of an addictive drug is increased, more people become addicted to and suffer the harms of that drug. Prescription opioids are as addictive as heroin, and the Defendants’ conduct in promoting increased supply and widespread access to prescription opioids has resulted in an epidemic of opioid addiction and overdose death.

- a. Addiction is the continued use of a substance despite harm to self and others and/or a desire to quit or cut back. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) uses the term “substance use disorder” to denote

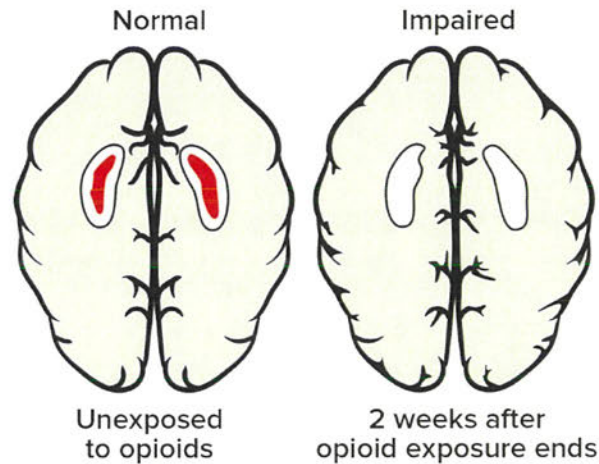
³⁹ *Id.* at p. 5.

⁴⁰ *Id.* at pp. 56-57.

⁴¹ Rayport M. Experience in the Management of Patients Medically Addicted to Narcotics. *JAMA - J Am Med Assoc.* 1954;156(7):684-691, at p. 690.

⁴² Lembke, “Drug Dealer, MD”, fn. 3, above, at pp. 56-57.

DOPAMINE ACTIVITY



- i. Exposure to/consumption of the addictive substance is a necessary criterion for the development of addiction to that substance. One of the biggest risk factors for becoming addicted to a substance is simple exposure to that substance.
- j. The current opioid epidemic is a tragic and compelling example of increased access leading to increased addiction and related death. The quadrupling of opioid prescribing between 1999 and 2012, combined with widespread distribution of those opioids to every corner of America, does not merely correlate with rising rates of opioid addiction and related deaths, it is causative.
 - i. A Task Force appointed by the Association of Schools and Programs in Public Health (ASPPH), issued a Report on November 1, 2019, concluding, “The *tremendous expansion of the supply* of powerful (high-potency as well as long-acting) prescription opioids led to scaled increases in prescription opioid dependence, and the transition of many to illicit opioids, including fentanyl and its analogs, which have subsequently driven exponential increases in overdose.”⁵⁵ The report also stated that addiction, or Opioid Use Disorder, “is caused by repeated exposure to opioids.”⁵⁶ ASPPH consists of over 120 member institutions accredited by the Council on Education for Public Health, including programs throughout the United States.⁵⁷ The Task Force was appointed by the ASPPH board of directors, and was composed of 14 “recognized experts in the field.” I agree with these statements of the ASPPH Task Force, which are consistent with, and supportive of, the opinions I have expressed in this Report, and in my work prior to becoming involved in litigation related to the opioid epidemic.

⁵⁵ ASPPH Report, “Bringing Science to Bear on Opioids,” fn.24, above, at p. 8 (emphasis added).

⁵⁶ *Id.* at p. 10.

⁵⁷ *Id.* at pp. 2-3, 56.

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- ii. In their 2017 report “Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use,” The National Academies of Science, Engineering and Medicine (NASEM) cited “heavy promotion of opioid prescribing by drug manufacturers (including misleading claims by some) and substantially increased prescribing” as contributors to the widespread availability and exposure to prescription opioids.⁵⁸
- iii. The NASEM Report also found that diversion is a key contributor to increased exposure to prescription opioids. Prescription drugs are diverted to nonmedical use in several ways: (1) diversion before a prescription has been filled (*e.g.*, theft from production facilities or retail pharmacies), (2) diversion via the filling of a prescription (*e.g.*, pursuant to doctor shopping and high-frequency prescribers, etc.) and (3) diversion after a prescription has been filled (*e.g.*, by subsequent transfer or sale to a third party). “The DEA (2016b, p. 34) reports that in recent years, distributors in the United States disbursed 12-15 billion dosage units of opioid narcotics to retail-level purchasers, suggesting that total diversion is on the order of 2.5-4.0 billion dosage units.”⁵⁹ A *Washington Post* analysis of federal ARCOS data shows that from 2006-2014, more than 100 billion oxycodone and hydrocodone pills were delivered in the United States.⁶⁰ At the same rate of diversion reported by NASEM for the period it reviewed, that would represent diversion on the order of 15.8-25 billion pills during the nine year period from 2006-2014.
- iv. Likewise, decreased supply of addictive substances decreases exposure and risk of addiction and related harms. Two natural experiments in the last century tested and proved this hypothesis. The first was Prohibition, a nationwide constitutional ban on the production, importation, transportation, and sale of alcoholic beverages from 1920 to 1933, which led to a sharp decrease in the number of Americans consuming and becoming addicted to alcohol.⁶¹ (There were other unintended consequences of Prohibition, but the positive impact on alcohol consumption and related morbidity is widely under-recognized.) Second, many soldiers in Vietnam during the Vietnam

⁵⁸National Academies of Science Engineering and Medicine (NASEM). *Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use*, 2017. doi:10.17226/24781, at pp. 40-41 (emphasis added).

⁵⁹ *Id.* at p. 223.

⁶⁰ Steven Rich, Scott Higham and Sari Horwitz *More than 100 Billion Pain Pills Saturated the Nation over Nine Years*, *Washington Post*, January 14, 2020.

⁶¹ Hall W. What are the policy lessons of National Alcohol Prohibition in the United States, 1920-1933? *Addiction*. 2010. doi:10.1111/j.1360-0443.2010.02926.x, at p. 105.

War became addicted to opioids, most of whom stopped using opioids on their return to the United States, where access was limited.⁶²

- k. Opioids are different from other addictive substances for the following reasons:
 - i. They are sold as medicine, normalizing their use and propagating a misleading safety profile, with devastating consequences.
 - ii. They kill quickly, such that even a single exposure in an opioid naïve person can lead to death.
 - iii. They create a debilitating dependence such that painful withdrawal leads to a vicious cycle of drug-seeking and withdrawal, as discussed in Section §C.10 of this Report, below.

3. Opioid prescribing began to increase in the 1980s and became prolific in the 1990s and the early part of the 21st century, representing a radical paradigm shift in the treatment of pain and creating more access to opioids across the United States.

- a. Prior to 1980, doctors used opioid pain relievers sparingly, and only for the short term in cases of severe injury or illness, during surgery, or at the very end of life.⁶³ Doctors' reluctance to prescribe opioids stemmed from the legitimate concern that patients would get addicted.
- b. Opioid prescribing quadrupled between the 1990s and 2012, and dramatically increased in dose and duration. "By 2010, enough OPR [opioid pain relievers] were sold to medicate every American adult with a typical dose of 5 mg of hydrocodone every 4 hours for 1 month."⁶⁴
 - i. From 1996 to 2011 there was a 1,448% increase in the medical use of opioids, with increases of 690% from 1995 to 2004 and 100% from 2004 to 2011. Over the same time period, opioid misuse increased more dramatically: 4,680% from 1996 to 2011, with increases of 1,372% from 1996 through 2004 and 245% from 2004 to 2011. The number of patients seeking treatment for opioid use disorder in this time period, not including heroin, increased 187%, whereas treatment-seeking increased 87% for heroin, 40% for cannabis, and decreased 7% for

⁶² Robins LN, Davis DH, Nurco DN. How permanent was Vietnam drug addiction? *Am J Public Health*. 1974;64(12 Sup):38-43. doi:10.2105/AJPH.64.12_Suppl.38, at p. 40.

⁶³ Meldrum ML. Opioids and Pain Relief: A Historical Perspective (Progress in Pain Research and Management, V. 25). IASP Press; 2003, at pp. 195-199.

⁶⁴ Paulozzi LJ, Jones CM, Mack K a, Rudd R a. Vital Signs: Overdoses of Prescription Opioid Pain Relievers --- {United States}, 1999–2008. *MMWR Morb Mortal Wkly Rep*. 2011;60(43):1487-1492, http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6043a4.htm?s_cid=mm6043a4_w, at p. 1489.

analgesia for moderate to severe pain, only six cases (2.6%) of possible drug misuse were reported” and that the risk of patient addiction was “much smaller than commonly believed.”⁷²⁹ As discussed elsewhere in this report,⁷³⁰ there are numerous flaws in Portenoy’s study, which made it an unreliable indicator of the true risk of addiction to prescription opioids, including but not limited to (a) the study excluded patients with self-reported past or present substance or alcohol abuse, which is atypical of real-world populations of prescription opioid patients; (b) the claim of a 2.6% rate of problematic use was based on an inappropriate denominator consisting of the entire population of 233 patients that started the study, without accounting for the 127 (>50%) of patients who dropped out of the study or were terminated by Purdue, the study sponsor; (3) the average daily dose was 52.5 mg of oxycodone (or 78.75 MME), which is lower than many real-world patients received, and the risk of addiction increases with higher dose; (4) 76% of the study participants had demonstrated prior acceptance of opioid therapy by participation in previous studies, which would not be true in a real-world patient population; and (5) many other prior and contemporaneous studies had shown far higher rates of addiction (up to 35%), but the Purdue-sponsored CE presentation to the pharmacists made no mention of those important data.⁷³¹

- iv. Albertsons, in collaboration with the NACDS worked for years to eliminate, limit, and delay national and state mandates to target the opioid oversupply and the opioid epidemic.
 - A. In 2016, the NACDS asked Albertsons to send a form letter asking members of the U.S. Congress to oppose mandating pharmacists to check the PDMP in the CARA Act.⁷³² Albertsons’ Anthony Provenzano responded internally that he would send out letters to “targeted legislators” and added, “[i]f checking the PDMP is to be mandated, it makes more sense to have it done as early as possible in the process (at the prescriber level), and if it is mandated at the prescriber level, it

⁷²⁹ JAN-MS-00477197, at -7198.

⁷³⁰ See §C.8.m., §C.8.p. and Appendix I.C. for further discussion of Portenoy (2007).

⁷³¹ Portenoy, “Long Term Use of Controlled-release Oxycodone”, fn. 728, above, at Figure 1 and p. 291.

⁷³² ALB-MDLCT9-00021138 at -1139.

is merely duplicative and waste of time to repeat it again at the pharmacy level.”⁷³³

- B. This statement completely ignores that pharmacists have an independent, corresponding responsibility to ascertain that controlled substances are dispensed for a legitimate purpose.⁷³⁴ Nonetheless, Albertsons and NACDS were successful in the effort to eliminate and delay a national pharmacy PDMP mandate: “At NACDS’ request, the draft agreement [for the CARA Act] does not include the Senate mandate for a state, in order to be eligible for grant funding, to require a dispenser to check the PDMP for controlled substance prescriptions.”⁷³⁵
- C. In March 2017, NACDS’ Mary Staples sent an email regarding a Texas Senate Bill 1412 that “would mandate that pharmacists check the PDMP prior to dispensing a prescription for an opioid, benzodiazepine, barbiturate or carisoprodol.”⁷³⁶ The email included NACDS’ suggested amendment that added that pharmacist only had to “use professional judgment based on prevailing standard of practice” in determining whether to check the PDMP.⁷³⁷ Staples noted “Ideally, we need to try to eliminate the mandate for pharmacists to check entirely or significantly limit the mandate.”⁷³⁸
- D. In response, Safeway’s (Albertsons) Julie Spier replied, “You really are the best!” and “You are appreciated!” to Staples,⁷³⁹ and internally commented to Albertsons colleague Laura Churns, “;-) ... Got to love Mary!”⁷⁴⁰ Along with her email Staples also forwarded a “one pager we can use with legislators”⁷⁴¹ that outlined NACDS’ arguments against a mandate including that it would be “incredibly burdensome” and “put pharmacists in the position of second-guessing the decisions of prescribers...”⁷⁴² Despite these arguments, Julie Spier commented to her Albertsons colleagues, “[i]f RPh are

⁷³³ ALB-MDLCT9-00021138

⁷³⁴ Purpose of issue of prescription, 21 C.F.R. §1306.04.

⁷³⁵ ALB-MDLCT9-00200564 at – 0565.

⁷³⁶ ALB-MDLCT9-00159690

⁷³⁷ *Id.*

⁷³⁸ *Id.* at 9691.

⁷³⁹ ALB-MDLCT9-00159687

⁷⁴⁰ ALB-MDLCT9-00159690

⁷⁴¹ *Id.* at -9691.

⁷⁴² ALB-MDLCT9-00159694

not using [the PDMP] on a regular basis they probably need to get this into their routine...opioids are a hot topic.”⁷⁴³

- E. A separate NACDS email discussing the PDMP bill, noted “NACDS’ policy is to oppose mandatory checking by pharmacists. We have been successful in other states carving out or limiting when pharmacists are required to check as there are only 7 states that have adopted limited requirements on when pharmacists must check...”⁷⁴⁴
- F. On March 28, 2017, the NACDS sent a letter to the Texas Senate on behalf of its members including Albertsons, repeating the argument that a mandate would “put pharmacists in the position of second-guessing the decisions of physicians” and suggested checking the PDMP only in the presence of certain red flags.⁷⁴⁵
- G. Notwithstanding these lobbying efforts, a version of the mandate passed the Texas legislature in 2017, requiring pharmacists to access the PDMP before dispensing opioids, benzodiazepines, barbiturates, and carisoprodol, starting on September 1, 2019.⁷⁴⁶
- H. In May 2018, the NACDS drafted a letter to Texas lawmakers asking them to extend the effective date of the mandate by one year, to September 1, 2020.⁷⁴⁷ In the draft letter, the NACDS argued that compliance with the mandate would require millions of hours to run PDMP reports and pharmacies needed time to integrate the PDMP check into the pharmacy workflow to minimize the added time burden.⁷⁴⁸
- I. Albertsons’ Laura Churns replied to the draft, “Albertsons supports the letter, as written, requesting a 1-year extension.”⁷⁴⁹ Internally, Churns asked if Albertsons would have an “in-workflow solution by 9/1/20?” to which Albertsons’ Director of Pharmacy Systems and Process Redesign, Marc E. Allgood, replied “regardless of systems,

⁷⁴³ ALB-MDLCT9-00111235

⁷⁴⁴ ALB-MDLCT9-00007084

⁷⁴⁵ ALB-MDLCT9-00157446

⁷⁴⁶ ALB-MDLCT9-00110533, ALB-MDLCT9-00279809 at -9810, and ALB-MDLCT9-00279812 at 9819.

⁷⁴⁷ ALB-MDLCT9-00009578 and ALB-MDLCT9-00009580.

⁷⁴⁸ ALB-MDLCT9-00009580

⁷⁴⁹ ALB-MDLCT9-00009576

we should have a solution that can be added to [the] workflow to review PDMP.”⁷⁵⁰

- J. On May 22, 2018, NACDS held a conference call to discuss the mandatory PDMP check issue which resulted in a revised letter to lawmakers advocating for both a one-year extension and that the mandate only require pharmacists to check “*NEW*” prescriptions for opioids, benzodiazepines, barbiturates, or carisoprodol.”⁷⁵¹
- K. These efforts appear to have been at least partially successful as the regulation was amended to change the effective date of the mandate to March 1, 2020.⁷⁵²
- L. Despite not being required by Albertsons policies, as discussed below, checking of the PDMP has been required in Texas since 2020, “Effective March 1, 2020, a pharmacist before dispensing an outpatient prescription for an opioid, benzodiazepine, barbiturate, or carisoprodol for a patient shall consult the Texas Prescription Monitoring Program (PMP) database to review the patient’s controlled substance history.”⁷⁵³ This mandatory checking requirement is essential for pharmacists to exercise their corresponding responsibility to protect against misuse and diversion of controlled substances, without which red flags are inevitably overlooked. Mandatory PDMP registration for prescribers and pharmacists is associated with a decrease in patients’ mean daily opioid dosage in MME and a lower percentage of patients dispensed high-dose opioid prescriptions above <90 MME.⁷⁵⁴
- v. Defendant Rite Aid Pharmacy collaborated with the APF to create a patient-facing educational pamphlet on pain. In the pamphlet itself, Rite Aid described its collaboration with the APF as follows: “As Rite Aid continues its mission of ensuring that customers receive the kind of information and services that really make a difference, the American Pain Foundation has been an invaluable resource.”⁷⁵⁵ The pamphlet

⁷⁵⁰ ALB-MDLCT9-00008770

⁷⁵¹ ALB-MDLCT9-00197420 and ALB-MDLCT9-00197422 (Emphasis in original).

⁷⁵² ALB-MDLCT9-00004502

⁷⁵³ Texas Administrative Code RULE §315.15

⁷⁵⁴ Castillo-Carniglia A, *et al.* Changes in opioid prescribing after implementation of mandatory registration and proactive reports within California’s prescription drug monitoring program. *Drug Alcohol Depend.* 2021;218:1-16, at pp. 6, 7.

⁷⁵⁵ PAIN RELIEF GUIDE: Tips and advice from your pharmacist. Rite Aid Pharmacy.

<https://docplayer.net/12194913-Pain-relief-guide-tips-and-advice-from-your-pharmacist.html> ; See Perrone, M. Pro-painkiller echo chamber shaped policy amid drug epidemic. September 19, 2016 Updated — December 15, 2016 at

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in Georgia, it was “not the norm” to check the PDMP before dispensing controlled substances.¹¹⁷²

- xiv. Also as of August 11, 2023, at Publix, the more controlled substances filled, the more money pharmacists and pharmacy team members earn,¹¹⁷³ because controlled substances are still included when calculating script count, volume, or store profitability measures for the purposes of pharmacist bonus calculations.¹¹⁷⁴ These types of financial incentives to dispense more prescriptions inherently conflict with the need to detect and resolve red flags.
- xv. From May 2006 through May 2019, Publix filled 752,246 opioid prescriptions, representing 31,789,759 dosage units, to Cobb County residents. According to Plaintiff’s red flag analysis, of those, 337,882 prescriptions triggered at least one red flag; 140,276 triggered at least two red flags; 57,550 triggered at least three red flags; and 23,048 triggered at least four red flags.¹¹⁷⁵
- q. Defendant Albertsons failed to effectively control against diversion and undermined the efforts of Pharmacists to prevent diversion.
 - i. Although, Albertsons claims to have had national dispensing policies and procedures for all times it owned and operated pharmacies, it could not produce any copies of national policies and procedures prior to 2013,¹¹⁷⁶ including no policies or procedures that addressed red flags.¹¹⁷⁷
 - A. In July 2013, Albertsons’ issued a document titled “Appropriate Dispensing of Controlled Substances,”¹¹⁷⁸ which identifies eleven “red flags that may warn a pharmacist that additional research is warranted.”¹¹⁷⁹ Of note, this document was not part of Albertsons’ official policies and procedures.
 - B. The red flags included in this document were paying in cash, opioid/benzodiazepine/muscle relaxant “cocktails,” patients residing outside locale of store and/or prescriber, prescriber writing frequent prescriptions for same drug, quantity, and

¹¹⁷² PUBLIX-MDLT8-00074321.

¹¹⁷³ Burckhalter Dep. at 176:19-176:24.

¹¹⁷⁴ PUBLIX-MDLT8-00059249.

¹¹⁷⁵ Plaintiff’s CT8 Amended and Superseding Red Flag Analysis served September 19, 2023, pursuant to Section D.2 of CMO.

¹¹⁷⁶ Covaci 30(b)(6) Dep. at 32:8-33:10.

¹¹⁷⁷ Covaci 30(b)(6) Dep. 38:11-15.

¹¹⁷⁸ Covaci 30(b)(6) Dep. Exhibit 3 (ALB-NM00015258 at -5259)

¹¹⁷⁹ Covaci 30(b)(6) Dep. Exhibit 3 (ALB-NM00015258)

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strength for multiple patients (aka “pill mills”), prescriptions outside the scope of the prescriber’s practice, patients requesting brand name products, shared addresses by patients presenting the same or similar prescriptions from the same prescriber, patients receiving large quantities of controlled substances, patients commonly presenting prescriptions on weekends or late in the day, new patients who have been turned away from other pharmacies, and evidence of patients having been prescribed controlled substances by multiple prescribers (aka “doctor shopping”).¹¹⁸⁰ According to the July 2013 document “[i]f one or more red flags exist, the pharmacist must exercise professional judgment in deciding whether to dispense and use available resources, as necessary and appropriate” including referring to the state’s Prescription Drug Monitoring Program (PDMP).¹¹⁸¹ Of note, discount cards for opioids were not included in the list of red flags.

- C. While this document was communicated to pharmacists,¹¹⁸² its substance was not added to Albertsons’ official policies and procedures in 2013.¹¹⁸³ As such, Albertsons could not hold pharmacists accountable for reviewing red flags, for example through reeducation or termination.¹¹⁸⁴

- ii. Albertsons’ Vice President of Pharmacy Compliance, Anthony Provenzano, argued in a letter to the New Hampshire U.S. Assistant Attorney that because “this guidance wasn’t formally incorporated into policy until February 28, 2016,” pharmacists did not violate Albertsons’ internal policy in failing to consider red flags for thirteen fraudulent prescriptions filled from December 1, 2013 to July 31, 2014.¹¹⁸⁵

- A. In the same letter, Provenzano claimed that the fraudulent prescriptions were filled “early on in the nation’s consciousness about the opioid crisis” and that “Terminology referencing the opioid epidemic as a ‘crisis’ did not appear

¹¹⁸⁰ Covaci 30(b)(6) Dep. Exhibit 3 (ALB-NM00015258 at 15259)

¹¹⁸¹ Covaci 30(b)(6) Dep. Exhibit 3 (ALB-NM00015258 at 15259)

¹¹⁸² Covaci Dep. Exhibit 14 (ALB-NM00038105 at 38122)

¹¹⁸³ Covaci 30(b)(6) Dep. 56:15-57:9.

¹¹⁸⁴ Covaci 30(b)(6) Dep. 83:4-84:4.

¹¹⁸⁵ ALB-MDLCT9-00005613, Provenzano Dep. 221:10-25, Provenzano Dep. Exhibit 8 (ALB-NM00144238). Although the letter was focused on New Hampshire, Provenzano forwarded the text of the letter to Albertsons’ Director of Pharmacy Systems and Process Redesign, Marc Allgood, saying, “similar arguments could be made for other states in all likelihood.” *Id.*

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until 2015, and it was not declared a public health emergency until 2017.”¹¹⁸⁶

B. Provenzano seems to be arguing that awareness of the opioid crisis was so nascent during the time that Albertsons filled the fraudulent prescriptions, as to render them not responsible. In fact, at the time Albertsons was filling the fraudulent prescriptions, the opioid epidemic was a widely recognized public health problem with more than a decade’s worth of media reports,¹¹⁸⁷ government reports,¹¹⁸⁸ CDC publications,¹¹⁸⁹ and a best-selling book,¹¹⁹⁰ documenting and publicizing the continuing crisis of prescription opioid overdose, abuse, diversion, and death. Furthermore, Albertsons was aware of Purdue’s 2007 guilty plea¹¹⁹¹ for criminal charges relating to the fraudulent marketing of OxyContin and DEA enforcement actions against pharmacies for failure to investigate or resolve red flags related to opioid dispensing.¹¹⁹²

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C. Albertsons paid \$30,000 to resolve the allegations in dispute in the letter.¹¹⁹³

8 & 8

iii. In November 2013, Albertsons issued “Retail Pharmacy ARx Policies and Procedures.” The document notes “[f]ederal law assigns pharmacists and prescribers corresponding responsibility to recognize and prevent diversion and abuse of controlled substances,” but does not discuss red flags or prescription drug monitoring programs (PDMPs).¹¹⁹⁴ Without the inclusion of red flags or PDMPs, the official

¹¹⁸⁶ ALB-MDLCT9-00005613

¹¹⁸⁷ GAO (2003), “OxyContin Abuse and Diversion”, fn. 403, above, at p. 2 and 9.

¹¹⁸⁸ State of Maine Substance Abuse Services Committee, “OxyContin Abuse: Maine’s Newest Epidemic” (2002), https://llec.mainelegislature.org/Open/Rpts/rml46_7_o99_2002.pdf; see also: GAO (2003), “OxyContin Abuse and Diversion”, fn. 403, above.

¹¹⁸⁹ CDC (2011), “Prescription Painkiller Overdoses in the US infographic”, fn. 67, above; Paulozzi (2011), “Overdoses of Prescription Opioid”, fn. 64, above; Paulozzi L, et al. CDC Grand Rounds: Prescription drug overdoses – a U.S. epidemic. *MMWR Morb Mortal Wkly Rep.* 2012;61(1):1-37.

¹¹⁹⁰ Meier B. Pain Killer: A Wonder Drug’s Trail of Addiction and Death. St. Martin’s Press; 2003.

¹¹⁹¹ See §C.6.j.xviii

¹¹⁹² *East Main Street Pharmacy*; Affirmance of Suspension Order, 75 Fed. Reg. 66,149, (Oct. 27, 2010). (Which described misconduct in 2005-2006 as the basis for DEA enforcement.). See additional discussion at §C.X.g., above.

¹¹⁹³ U.S. Attorney’s Office, District of New Hampshire. (2019, September 9). *Two Pharmacy Chains Pay Civil Monetary Penalties to Resolve Alleged Violations of the Controlled Substances Act* [Press release]. <https://www.justice.gov/usao-nh/pr/two-pharmacy-chains-pay-civil-monetary-penalties-resolve-alleged-violations-controlled>

¹¹⁹⁴ Covaci 30(b)(6) Dep. Exhibit 4 (ALB-NM00006764 at -6818)

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policies and procedures provided Albertsons pharmacists with minimal guidance on what circumstances require further investigation of a prescription. Also, while this policy document includes a section of state specific policies (e.g. California and Florida), there were no state-specific policies provided for Texas.¹¹⁹⁵

- iv. In the same month in 2013 (November) that Albertsons issued the policies and procedures without mention of red flags, Lynette Berggren, Albertsons Director of Compliance, Privacy and Pharmacy,¹¹⁹⁶ sent an email highlighting the need to resolve every red flag.¹¹⁹⁷
- A. Berggren reported to Bobbie Riley on a presentation¹¹⁹⁸ given by two former DEA attorneys to the American Society for Pharmacy Law (ASPL) 2013 Developments in Pharmacy Law Seminar XXIV,¹¹⁹⁹ noting “They had some very interesting things to say about the positions the DEA has taken on how they interpret ‘corresponding responsibility,’ including the need for a pharmacist to absolutely resolve each and every ‘red flag’ (which continue to evolve) prior to filling a CS prescription. It was very interesting, but honestly a little disturbing given some of our recent inquiries.”¹²⁰⁰
 - B. Berggren forwarded the presentation, which included discussion of *Holiday CVS*,¹²⁰¹ recommended, “Use the PDMP” as a method to resolve red flags,¹²⁰² and noted continued deference to the DEA by courts in criminal cases regarding the requirement to conclusively resolve red flags.¹²⁰³
 - C. The presentation listed numerous red flags that were not included in Albertsons July 2013 document on red flags, such as: “the number of dosage units prescribed,” “the duration and pattern of alleged treatment,” “requests for early refills,” another pharmacist who refused “to fill prescriptions issued by a particular prescriber,” family members receiving

¹¹⁹⁵ Covaci 30(b)(6) Dep. Exhibit 4 (ALB-NM00006764 at -6906-6926)

¹¹⁹⁶ Lynette Berggren. [LinkedIn page]. <https://www.linkedin.com/in/lynette-berggren/>

¹¹⁹⁷ ALB-MDLCT9-00192578

¹¹⁹⁸ ALB-MDLCT9-00192580

¹¹⁹⁹ American Society for Pharmacy Law. *2013 Developments in Pharmacy Law Seminar XXIV* [Brochure]. https://www.aspl.org/assets/Conferences/dplXXIV_2013/reg_broch_aspl2013.pdf

¹²⁰⁰ ALB-MDLCT9-00192578

¹²⁰¹ ALB-MDLCT9-00192580 at -2596-2598. See further discussion of *Holiday CVS* at §C.6.j.xii

¹²⁰² *Id.* at -2611.

¹²⁰³ *Id.* at -2615.

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“prescriptions for controlled substances from the same prescriber,” and “lack of doctor patient relationship.”¹²⁰⁴

- D. In 2013, Albertsons was aware of the DEA position on red flags, the utility of the PDMP, and had generated a specific list detailing red flags, yet failed to educate their own pharmacists with this information or create adequate policies and procedures to allow pharmacists to act on this information.
- v. In February 2016, Albertsons’ “Retail Pharmacy Policies and Procedures” were updated to provide that seventeen “red flags must be considered individually and in any combination and in consideration of the overall facts and circumstances.”¹²⁰⁵
- A. Although, Albertsons had previously provided a list of red flags to pharmacists, this was the first time they were formally included in its policies and procedures. Albertsons required pharmacists to “seek additional information to verify the legitimacy of the prescription and exercise professional judgment in determining whether the prescription may be lawfully dispensed.”¹²⁰⁶
- B. However, the five steps it provided to fulfill this requirement were not mandated, including not mandating talking with the prescriber, reviewing patients’ dispensing history, or checking the state’s prescription drug monitoring program,¹²⁰⁷ leaving the door open to skipping these basic and necessary steps to investigating red flags. Pharmacists were required only to document “[a]ll inquiries that result in the pharmacist’s decision to fill a prescription, despite the existence of red flags...”¹²⁰⁸ *decision to fill*
- vi. Later, in September 2016, an internal slide deck titled “Changing Engines in Flight” was presented at an Albertsons “[Director of Pharmacy Operations] Meeting.”¹²⁰⁹ Included in the presentation is a slide that identifies “Script growth” as one of a few “Keys to Success.”¹²¹⁰

¹²⁰⁴ *Id.* at -2604-2610.

¹²⁰⁵ Covaci 30(b)(6) Dep. Exhibit 5 (ALB-NM00007961 at -8034)

¹²⁰⁶ Covaci 30(b)(6) Dep. Exhibit 5 (ALB-NM00007961 at -8034)

¹²⁰⁷ Covaci 30(b)(6) Dep. Exhibit 5 (ALB-NM00007961 at -8035)

¹²⁰⁸ Covaci 30(b)(6) Dep. Exhibit 5 (ALB-NM00007961 at -8035)

¹²⁰⁹ Covaci 30(b)(6) Dep. 118:7-19; Exhibit 9 (ALB-NM00015374 at -5375)

¹²¹⁰ Covaci 30(b)(6) Dep. Exhibit 9 (ALB-NM00015374 at -5460)

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- A. Jessica Covaci confirmed that “Script Growth” referred to increasing the number of prescriptions as a key to its success, including controlled substances: “We’re a business... We’ve got to grow.”¹²¹¹ Although growing a business is a legitimate endeavor, doing so at the expense of public health is not.
- B. This slide follows another which appears to identify an over ~~opportunity~~ opportunity” by increasing prescriptions and ~~reducing~~ pharmacist hours.¹²¹² By reducing pharmacists’ hours, Albertsons would make it more difficult for pharmacists to fulfill their corresponding responsibility, including talking with the prescriber, reviewing the patients’ dispensing history, or checking the PDMP. Albertsons policies and procedures repeatedly emphasized the professional judgment of the individual pharmacist, but without giving them the necessary support or information to exercise professional judgment, Albertsons pharmacists would not have been able to exercise their informed judgment.
- vii. In April 2018, Anthony Provenzano sent an email on “Options to address the Opioid Crisis,” including mandatory education for pharmacists on appropriate dispensing.¹²¹³ Provenzano testified that Albertsons “already had controlled substance training, but it didn’t focus as much about dispensing, more about the loss prevention....”¹²¹⁴ Loss prevention refers to pharmacy theft, a distinct and separate problem from pharmacists exercising their corresponding responsibility to prevent misuse and diversion.
- viii. In September 2018, Albertsons again updated its pharmacy policies and procedures. It again provided seventeen red flags, but revised the options pharmacists “may consider” to verify the legitimacy of a prescription.¹²¹⁵
- A. In this iteration, pharmacists were now required to register or be approved to access their states’ PDMP and to check the “PDMP when circumstances exist that cause the pharmacist to question the validity or appropriateness of the prescription.”¹²¹⁶

↓ hours

1.) Mandatory education

¹²¹¹ Covaci 30(b)(6) Dep. 126:8-127:9; 133:2-7

¹²¹² Covaci 30(b)(6) Dep. Exhibit 9 (ALB-NM00015374 at -5459)

¹²¹³ Provenzano Dep. Exhibit 4 (ALB-NM00063312)

¹²¹⁴ Provenzano Dep. 130:8-131:24.

¹²¹⁵ Covaci 30(b)(6) Dep. Exhibit 6 (ALB-NM00009720 at -9795-9796)

¹²¹⁶ Covaci 30(b)(6) Dep. Exhibit 6 (ALB-NM00009720 at -9796)

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- B. This new requirement was consistent with Albertsons Pharmacy Compliance Meeting Minutes from the same month, which noted that the “PDMP is identified as the low hanging fruit and will be used by DEA as a tool for determining inappropriate dispensing.”¹²¹⁷
 - C. Importantly, Albertson’s policy inverted the proper sequence of investigating red flags, since review of the PDMP is often necessary to reveal red flags in the first place, such as multiple prescribers or dispensers, dangerous drug-drug combinations, and patterns of early refills. It is illogical to only investigate the PDMP after having detected suspicious circumstances by other means, and this inverted sequence almost certainly assured that red flags would be missed.
- ix. In January 2019, Albertsons policies and procedures nearly doubled the red flags listed to thirty-two and noted, “whether or not listed, any situation that causes a pharmacist to question the validity or legitimacy of a prescription should be treated as a red flag.”¹²¹⁸
- A. The policy was also revised to identify specific categories of red flags: presentation of the prescription (e.g. “The patient asks for drugs using slang or street terms” or “Patient presents a handwritten prescription that looks altered...”), patient behavior, medication taking/supply, prescriber concerns, and illicit/illegal conduct.¹²¹⁹
 - B. The policy again required mandatory checking of the PDMP only “when circumstances exist that cause the pharmacist to question the validity or appropriateness of the prescription.”¹²²⁰ Documentation was only required for PDMP “inquiries that result in the pharmacist's decision to fill or not fill a prescription when red flags are observed...”¹²²¹
- x. In January 2020, Albertsons provided another update to its retail pharmacy policies and procedures.¹²²² For the first time the policy

¹²¹⁷ Provenzano Dep. Exhibit 5 (ALB-NM00126515 at -6516)

¹²¹⁸ Covaci 30(b)(6) Dep. Exhibit 7 (ALB-NM00009964 at -10040-10041)

¹²¹⁹ Covaci 30(b)(6) Dep. Exhibit 7 (ALB-NM00009964 at -10040-10041)

¹²²⁰ Covaci 30(b)(6) Dep. Exhibit 7 (ALB-NM00009964 at -10041-10042)

¹²²¹ Covaci 30(b)(6) Dep. Exhibit 7 (ALB-NM00009964 at -10042)

¹²²² ALB-MDLCT9-00245743

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explicitly required that red flags “must be resolved to the pharmacist’s satisfaction prior to dispensing.”¹²²³

- A. The new policy updated the language regarding checking the PMDP to add reference to red flags and diversion: “the pharmacist must query and assess PDMP information if the pharmacist has any reason, based on professional judgment *and consideration of red flags*, to question the validity or appropriateness of the prescription or *whether it will be used for purposes other than to treat a diagnosed condition*.”¹²²⁴
- B. However, as shown, the policy only required checking the PDMP when certain circumstances arose and not whenever a controlled substance (including opioids) was dispensed.¹²²⁵
- C. The most recent update to the policies and procedures I have seen, from April 2021, retains this same language.¹²²⁶ The 2021 update did add for the first time that not only must red flags be resolved, but they also must be documented.¹²²⁷
- D. Although Albertsons required documentation of measures taken to determine the legitimacy of a prescription, it did not direct where documentation must occur, making it difficult to know where to find the information.¹²²⁸ Even today, there are multiple places where documentation can occur including on the hard copy paper prescription, in the electronic prescription notes field, in patient profiles, and in the “fill notes section” in Albertsons system.¹²²⁹ Albertsons requires pharmacists to review the patient profile but not other forms of documentation, and there is no centralized system for collecting disparate datapoints for documenting red flags, such that pharmacists could miss key pieces of information regarding red flags.¹²³⁰

- xi. The policies and procedures discussed above were noted in a July 2019 internal presentation of a list of items “already in place” as part of Albertsons’ “COMPANY RESPONSE TO OPIOID CRISIS.” Included

¹²²³ *Id.* at -5819.

¹²²⁴ *Id.* at -5821. (emphasis added)

¹²²⁵ *Id.* at -5821.

¹²²⁶ ALB-MDLCT9-00360462 at -0540.

¹²²⁷ ALB-MDLCT9-00360461 and ALB-MDLCT9-00360462 at -0539.

¹²²⁸ Covaci 30(b)(6) Dep. 60:14-62:5

¹²²⁹ Covaci 30(b)(6) Dep. 62:11-63:1

¹²³⁰ Covaci 30(b)(6) Dep. 67:8-68:15

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in the items was “controlled substance trainings” and “Appropriate dispensing of controlled substances communications.”¹²³¹

- A. However, the same presentation slide also noted that Albertsons still had not completed a “comprehensive [controlled substance] training program,” which Jessica Covaci testified did not occur until “late 2019, early 2020.”¹²³²
 - B. Covaci described the training as including “everything about controlled substances from a regulatory and compliance perspective...everything from record keeping, to loss reporting, to identifying red flags, to how to use a PDMP...how to navigate conversations with prescribers and patients in addressing those situations where there were questions about a patient's particular therapy and the appropriate professional course of action to take in those interactions, how to calculate morphine milligram equivalence and how that played in with the CDC's guidelines that they published.”¹²³³ July 2019 is late to be providing training for an epidemic that had begun two decades earlier.
- xii. Albertsons failed to monitor problematic prescribers or patients at the corporate level. Albertsons did not track red flag information documented by its pharmacists,¹²³⁴ such as pharmacists refusing to fill certain prescriptions,¹²³⁵ prescribers writing illegitimate prescriptions,¹²³⁶ or patients trying to fill illegitimate prescriptions.¹²³⁷ Consequently, doctors who had been blocked by other pharmacies continued to have prescriptions filled by Albertsons, a practice that went on for years.
- xiii. In 2019, Dr. Howard Diamond of Sherman, Texas was sentenced to twenty years in federal prison for illegal distribution of opioids between 2010 and 2017.¹²³⁸
- A. In July 2014, Albertsons Southern Division Director of Pharmacy Operations, Julie Spier reported that other chain

¹²³¹ Covaci Dep. Exhibit 14 (ALB-NM00038105 at 38111)

¹²³² Covaci Dep. 174:11-18; Covaci Dep. Exhibit 14 (ALB-NM00038105 at 38111)

¹²³³ Covaci Dep. 173:6-22.

¹²³⁴ Covaci 30(b)(6) Dep. 101:20-103:12

¹²³⁵ Covaci 30(b)(6) Dep. 100:8-19

¹²³⁶ Covaci 30(b)(6) Dep. 100:20-101:3

¹²³⁷ Covaci 30(b)(6) Dep. 103:22-104:3

¹²³⁸ U.S. Attorney's Office, Eastern District of Texas. (2019, May 9). *Two North Texas Doctors, One Nurse Sentenced to Prison for Federal Drug Trafficking Violations* [Press release]. <https://www.justice.gov/usao-edtx/pr/two-north-texas-doctors-one-nurse-sentenced-prison-federal-drug-trafficking-violations>

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pharmacies had stopped filling Dr. Diamond's prescriptions.¹²³⁹ A February 2014 Kroger internal email shows a "Do Not Fill Controlled Substance RX For This Prescriber" put in place to block Dr. Diamond's prescriptions from being filled at Kroger.¹²⁴⁰ An internal Walmart email from November 2014 reported, "the corporate offices of Target and Kroger have told their pharmacists that they are not allowed to fill [controlled substances] from Dr[.] Howard Gregg Diamond at all period."¹²⁴¹ Another Walmart email from December 2014 reported that Dr. Diamond was under investigation by the DEA and Target, Walgreens, Kroger, and Medicine Shoppe would not fill prescriptions from Dr. Diamond, while confirming that Albertsons would continue to dispense after verifying patients in the Texas Department of Public Safety system and on a case-by-case basis.¹²⁴² A follow up to this email in February 2015, described Dr. Diamond's patients coming up to the pharmacy counter "3 at a time with methadone, norco, xanax, and sometimes ms contin, and then tell you he 'videochats' with them" as well as prescriptions for people living 100 miles away,¹²⁴³ illustrating several red flags, including patients coming in groups, dangerous drug-drug combinations, the potential lack of a legitimate doctor-patient relationship, and patients living far from the pharmacy in question.¹²⁴⁴

- B. Walmart instituted a corporate block of Dr. Diamond on March 2, 2017¹²⁴⁵ and the notice of the block was faxed to Albertsons Division Pharmacy Manager David Hicks on March 6, 2017.¹²⁴⁶ As a Division Pharmacy Manager, Hicks oversaw Albertsons pharmacies in the Dallas/Fort Worth metroplex area including Tarrant County.¹²⁴⁷

¹²³⁹ ALB-MDLCT9-00324713

¹²⁴⁰ Kroger-MDL00030302 at -0303.

¹²⁴¹ WMT_MDL_000536546 at -6547.

¹²⁴² WMT_MDL_000677382 at -7384.

¹²⁴³ WMT_MDL_000677382

¹²⁴⁴ Since the onset of COVID-19, video (telehealth) appointments between doctors and patients have become relatively common. However, as of 2015, telehealth was far less common in all areas of medicine and Dr. Diamond's use of "videochats" to prescribe opioids should have been an obvious red flag, along with his other inappropriate prescribing behaviors.

¹²⁴⁵ ALB-MDLCT9-00092444

¹²⁴⁶ ALB-MDLCT9-00092443

¹²⁴⁷ Deposition of David Hicks, *In Re: National Prescription Opiate Litigation* (MDL No. 2804, Track 9), July 19, 2023 (herein after "Hicks Dep."), at 18:12-20:19.

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- C. In May 2017, the DEA and FBI raided Dr. Diamond's office looking for patient and drug records, and in the month prior, Dr. Diamond acknowledged in a Facebook post that "Most of the pharmacies in my practice region, Sherman and Paris[,]Texas have stopped filling prescriptions for my patients.¹²⁴⁸ The exception was Albertsons, which continued to fill Dr. Diamond's prescriptions.
- D. In May 2017, Albertsons Division Pharmacy Manager David Hicks reported to Jessica Covaci that, "We have several pharmacies that have noticed some unusual prescribing habits with [Dr. Diamond]. As a result, I have recommended that several of our stores stop filling scripts for controlled substances from the Dr."¹²⁴⁹ Covaci responded that Albertsons would "evaluate central blocking."¹²⁵⁰
- E. A few days later, Hicks forwarded the article reporting on the raid of Dr. Diamond's offices.¹²⁵¹ In July 2017, Dr. Diamond was arrested on federal drug conspiracy charges, with the conspiracy having resulted in at least seven deaths across Texas and Oklahoma.¹²⁵²
- F. After the arrest, Hicks followed up with Covaci on July 12, 2017, sending a link to the article reporting the arrest and commenting, "Can we put in some kind of block on this doctor. He is in jail so I don't know if we'll get any more scripts from him but I don't know if we have things out there with refills or if a nurse may try to still call in stuff?"¹²⁵³
- G. Also on July 12, an internal Kroger email commented on the arrest, "I would call [Kroger's] decision to cut off his prescriptions several years ago a significant success for our compliance program, and in helping to protect the safety of the patients we serve, Now the question is who is the next Dr. Diamond and where did his patients go....."¹²⁵⁴

¹²⁴⁸ Zwirko, W. (2017, May 19). Feds raid doctor's offices in Sherman, Paris. *KTEN*. <https://www.kten.com/story/35474323/feds-raid-doctors-offices-in-sherman-paris>

¹²⁴⁹ ALB-MDLCT9-00091915

¹²⁵⁰ *Id.*

¹²⁵¹ *Id.*

¹²⁵² Knapp, R. (2017, July 12). Feds: Sherman doc misprescribed pain meds in seven overdose deaths. *KXII*. <https://www.kxii.com/content/news/Sherman-Paris-physician-arrested-on-federal-drug-charges-434065533.html>

¹²⁵³ ALB-MDLCT9-00332111

¹²⁵⁴ Kroger-MDL00030291

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- H. As described above, Dr. Diamond's patients went to Albertsons for years after Kroger and other chain pharmacies implemented corporate blocks and stopped filling his prescriptions, in contrast to Albertsons, who up to the date of his arrest still had not implemented a corporate block against him.
- xiv. In another example, on November 30, 2018, Walmart instituted a central prescriber block against Dr. Kenneth Anderson in Sherman, Texas.¹²⁵⁵
- A. In January 2019, a pharmacist at an Albertsons store #226 in Sherman, Texas reported to David Hicks that Dr. Anderson was "banned corporately from Walmart and CVS from filling."¹²⁵⁶ The pharmacist reported that the store was averaging "over 600 tabs/day just in 10/325" of hydrocodone and wanted corporate help with the situation.¹²⁵⁷
- B. Hicks replied, "I can tell you that getting anything blocked from corporate is going to be a slow process," and confirmed that there was never a corporate block on Dr. Diamond: "Technically we never blocked diamond on a corporate level but he just had such a bad reputation that stores had to do it individually."¹²⁵⁸
- C. Hicks relayed the report about Dr. Anderson to Julie Spier, "Not sure if you recall a Dr[.] Diamond from the Sherman area that was running a pill mill. He's in jail now but I think all his patients ended up with a Dr[.] Anderson. Now it appears this new doctor has some questionable prescribing habits.... CVS and Walmart have blocked all filling from this Dr... so now we're being flooded with new business, mostly controls/hydrocodone. Not sure this is the new business we are looking for. I've told the [pharmacist] about due diligence and [pharmacist] discretion, but this is a sensitive area. Will corporate ever do a company-wide block? Especially if customers start branching out to other stores?"¹²⁵⁹

¹²⁵⁵ WMT MDL 001071502

¹²⁵⁶ ALB-MDLCT9-00331761

¹²⁵⁷ *Id.*

¹²⁵⁸ *Id.*

¹²⁵⁹ ALB-MDLCT9-00331864

- D. In response to Hicks' request for a corporate block, Spier refused, noting that Albertsons leaves it up to the pharmacist to use their professional judgment to fill or not.¹²⁶⁰
- I. While Jessica Covaci testified that Albertsons corporate (not pharmacists) can block problematic prescribers, it blocked fewer than ten prescribers nationwide since 2015.¹²⁶¹
- II. Considering the problematic prescribers discussed above, ten prescribers is probably a serious undercount of the number of problematic prescribers that would have been identified if Albertsons' policies had been adequate, and in particular, if Albertsons had required its pharmacists to check the PDMP as part of their regular job duties.
- E. In August 2019, an Albertsons' District Pharmacy Manager in Portland forwarded an email from a Safeway (owned by Albertsons)¹²⁶² staff pharmacist to Covaci.¹²⁶³ The original email raised concerns about current and former Wal-Mart customers getting opioid prescriptions filled at their Safeway (Albertsons) pharmacy.¹²⁶⁴ The staff pharmacist noted, "patients come directly from the Wal-Mart pharmacy to our counter with their prescriptions after being told by the Wal-Mart that 'they follow the government guidelines when filling opioid prescriptions'. The inference is that we at Safeway do not and therefore will fill those prescriptions."¹²⁶⁵
- xv. Albertsons was aware of the rising tide of deaths caused by the opioid epidemic, but failed to take adequate action within its purview to stem the tide, including a failure to include a list of red flags for dispensing in its policies and procedures until 2019, a failure to educate pharmacists to identify, investigate, and document red flags of dispensing until 2019, a failure to create a system of documentation that would allow for information about red flags to be readily disseminated between pharmacists, a failure to mandate the PDMP until 2018, and then only after circumstances arose to question the validity or appropriateness of the prescription, thereby increasing the likelihood of overlooking red flags, and a failure to include opioid discount cards as a red flag until 2016 and to limit their use despite awareness of their

¹²⁶⁰ *Id.*

¹²⁶¹ Covaci Dep. 75:17-80:4

¹²⁶² Covaci Dep. 142:11-13, 145:2-7

¹²⁶³ Covaci Exhibit 11 (ALB-NM00144815)

¹²⁶⁴ Covaci Exhibit 11 (ALB-NM00144815 at -4816)

¹²⁶⁵ Covaci Exhibit 11 (ALB-NM00144815 at -4816)

contribution to the opioid epidemic. The actions Albertsons did take were reluctant, belated, and not in keeping with other chain pharmacies, who themselves failed to model good corporate citizenship. Albertsons hid behind the pharmacists “professional judgment” as a way of avoiding corporate responsibility. Without corporate leadership, support, and infrastructure, Albertsons’ individual pharmacists were greatly handicapped in their ability to exercise their clinical judgment or fulfill their corresponding responsibility.

- r. In summary, the Pharmacy Defendants were far more than unwitting pill dispensers. Instead, they actively participated in efforts to increase the opioid oversupply while ignoring the many warning signs of a growing opioid problem, and as such were central drivers of the opioid epidemic. As the “last line of defense” against opioid misuse and diversion, these Defendants failed.

7. No reliable scientific evidence shows that long-term opioid therapy is effective for chronic non-cancer pain.

- a. Through the aforementioned methods, and by relying on flawed and industry-backed studies, the Pharmaceutical Opioid Industry encouraged and promoted several misconceptions concerning opioid use, including overstatement of benefits of long-term use for chronic pain. In fact, there is not, and has never been, reliable evidence that long-term opioid use improves pain or function to any clinically meaningful degree.
- b. The best evidence available suggests that there is little or no improvement in pain or function for most patients on long-term opioid therapy. The Industry further claimed that the failure to prescribe opioids led to the “undertreatment of pain.” Whether or not pain was undertreated does not change the fact that prescription opioids are an inappropriate method to address that concern, due to the absence of evidence of long-term benefit, and the strong evidence of unacceptable risk.¹²⁶⁶ Patients often endorse ongoing subjective benefit from the opioid, not because it is treating underlying pain, but because it is relieving the pain of opioid withdrawal from the previous dose. Studies show that pain improves when patients on chronic high dose opioid therapy reduce their dose or come off opioids. Limiting opioid prescribing is good medicine, because it decreases exposure to a dangerous and potentially lethal drug, without compromising pain treatment. A detailed table and a summary demonstrative, below, summarize the lack of reliable evidence that prescription opioids are effective for chronic pain:

¹²⁶⁶ As stated in the NASEM 2017 Report, “The very real problems of underdiagnosis and undertreatment of pain are valid concerns, but *it would be a mistake to infer that greater utilization of opioids would ameliorate these problems*,” due to the lack of evidence that opioids provide long-term benefits for chronic pain. NASEM Report (2017), fn. 58, above, at p. 51. (emphasis added).

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trained to track opioid misuse and addiction: “Physicians are writing more opioid prescriptions, but they do not know how to monitor patients.”¹⁵⁷⁵

- C. Janssen’s own advisors conceded that even with training, it is extremely difficult to tell which patients will develop an opioid misuse problem: “Preliminary findings show that information or impressions gained in the doctor-patient relationship cannot predict which patients will have a positive urine toxicology screen. Even urine tox screens may not be reliable as they vary, and some have low sensitivities to oxycodone and fentanyl.”¹⁵⁷⁶
- D. Yet despite these tangible and openly recognized limitations, Defendants launched an aggressive marketing campaign targeting prescribers, which misrepresented the facts on risk of addiction and validity of screening, and instead aggressively promoted uptitrating of their products.¹⁵⁷⁷

9. Increased supply of prescription opioids contributed substantially to more individuals becoming addicted to opioids and transitioning from prescription opioids to illicit sources of opioids such as heroin and fentanyl (The Gateway Effect).

- a. There is a clear causal link between prescription opioid exposure, prescription opioid misuse, and opioid addiction. Opioid misuse, or non-medical use of prescription opioids (“NMUPO”)¹⁵⁷⁸, is defined as taking an opioid medication outside of a prescribed indication.¹⁵⁷⁹ With increased opioid prescribing in the United States, more Americans have been exposed to prescription opioids at higher doses and for longer durations (including those not directly prescribed the opioid), contributing to rising incidence and prevalence of opioid misuse, dependence, addiction, and overdose death.¹⁵⁸⁰ These are the expected and natural consequences of exposing large populations to addictive and dangerous drugs, particularly where tolerance requires users to increase the dose to achieve the same effect, resulting in ever-greater risk of harm.
- b. Teens are especially vulnerable to the increased access to prescription drugs. Adolescence is a time when the rapidly growing brain is more plastic, and therefore more vulnerable on a neurological level, to potentially irreversible brain changes caused by chronic drug exposure. Teens are also more likely to

¹⁵⁷⁵ *Id.* at 1062.

¹⁵⁷⁶ *Id.* at 1064.

¹⁵⁷⁷ See JAN-MS-00779345, FDA Warning Letter to Janssen, RE: NDA #19-813, September 2, 2004.

¹⁵⁷⁸ NMUPO is sometimes referenced as “NUPO”, nonmedical use of prescription opioids.

¹⁵⁷⁹ NASEM Report (2017), fn. 58, above, at p. 152.

¹⁵⁸⁰ *Id.* at p. 193

take risks, without appreciating the adverse consequences associated with those risks.¹⁵⁸¹

- c. In 2012, some 1.9 million individuals aged 12 or older misused a prescription drug for the first time within the past twelve months, an average of 1,350 initiatives per day. Prescription drugs now rank fourth among the most-misused substances in America, behind alcohol, tobacco, and cannabis. They rank second among teens. Of those who became addicted to any drug in the previous year, a quarter started out using a prescription medication: 17 percent began with opioid pain relievers, 5 percent with sedative-hypnotics, and 4 percent with stimulants.¹⁵⁸²
- d. In 2017, McCabe *et al.* found, “Adolescents who reported both medical and nonmedical use of prescription opioids were more likely to indicate medical use of prescription opioids before initiating nonmedical use...” (“NUPO”)¹⁵⁸³ “The findings provide compelling evidence that medical use of prescription opioids and NUPO are highly correlated, especially among adolescents. . . . We found that the majority of NUPO involved a history of medical use, and this finding should provide some concern to health professionals who prescribe opioid medications to adolescents, given the serious health consequences associated with NUPO.”¹⁵⁸⁴ McCabe’s reference for this point included the Compton (2016) article (cited in §9.h., below), that described the trajectory from non-medical use to illicit opioids, thus emphasizing that McCabe is referring to the “Gateway Effect” transition, i.e., from initial medical use, to subsequent non-medical use, and ultimately to illicit opioids.
- e. In 2019, McCabe *et al.* found that almost one in every two high school seniors who reported the medical use of prescription opioids after initiating NMUPO had two or more substance use disorder (addiction) symptoms at age 35.¹⁵⁸⁵
 - i. These data show that teens who are exposed to prescription opioids without a prescription will often be further exposed through a subsequent medical prescription, and as a result are at increased risk of developing an opioid addiction later in life (above what their risk would have been with non-medical use alone). The cumulative effect of

¹⁵⁸¹ Lembke, Drug Dealer MD, fn. 3, above, at pp. 26 and 48.

¹⁵⁸² *Id.* at pp. 25-26.

¹⁵⁸³ McCabe, Sean Esteban, *et al.* Trends in medical and nonmedical use of prescription opioids among US adolescents: 1976–2015. *Pediatrics* 139.4 (2017): e20162387, at p. 1.

¹⁵⁸⁴ *Id.* at p. 8.

¹⁵⁸⁵ McCabe SE, Veliz PT, Boyd CJ, Schepis TS, McCabe V V., Schulenberg JE. A prospective study of nonmedical use of prescription opioids during adolescence and subsequent substance use disorder symptoms in early midlife. *Drug Alcohol Depend.* 2019. doi:10.1016/j.drugalcdep.2018.10.027, at p. 379.

prescription opioid exposure, through both medical and non-medical use, causally leads to opioid addiction.¹⁵⁸⁶

- ii. The authors write, “These results indicate substantial risk for developing SUD among adolescents who have already initiated NMUPO and reinforce the critical role of screening when prescribing opioid analgesics to adolescents.”¹⁵⁸⁷ While the authors suggest that screening can play a role in mitigating future opioid addiction, screening tools have been shown to have limited efficacy in identifying at risk patients.¹⁵⁸⁸ The more significant goal is to reduce access to prescription opioids, which increases risk by increasing exposure to both medical and subsequent non-medical use.
- f. In 2020, McCabe *et al.* reported upon the longitudinal relationship between U.S. teens’ prescription opioid use (medical and non-medical) and subsequent heroin use in adulthood.¹⁵⁸⁹ From more than 11,000 survey respondents, they found that adolescents who reported *either medical use or non-medical use* of prescription opioids were at greater risk of progressing to heroin use in adulthood than population controls.¹⁵⁹⁰
 - i. The McCabe 2020 study definitively supports the conclusion that medical users of prescription opioids transition to heroin use, regardless of intervening non-medical use. In more recent cohorts in the population sample in the McCabe 2020 study, 7% of teens who reported prescription opioid medical use only went on to use heroin in adulthood, for an adjusted odds ratio of 2.68 (95% CI 1.01, 7.17).¹⁵⁹¹ This “compelling longitudinal data” showed that adolescents who reported medical use only of prescription opioids compared to adolescents who had never been exposed to prescription opioids “were nearly 3 times more likely to transition to heroin use in subsequent years.”¹⁵⁹²

¹⁵⁸⁶ *Id.* at p. 381.

¹⁵⁸⁷ *Id.* at p. 383.

¹⁵⁸⁸ Clark MR, Hurley RW, Adams MCB. Re-assessing the Validity of the Opioid Risk Tool in a Tertiary Academic Pain Management Center Population. *Pain Med.* 2018;19(7):1382-1395. <http://dx.doi.org/10.1093/pm/pnx332>, at p. 1382.

¹⁵⁸⁹ McCabe SE, Boyd CJ, Evans-Polce RJ, McCabe VV, Schulenberg JE, Veliz PT. From Pills to Powder: A 17-year transition from prescription opioids to heroin among US adolescents followed into adulthood. *J Addict Med.* 2021;15:241-244., at p. 241.

¹⁵⁹⁰ *Id.*

¹⁵⁹¹ *Id.* at Table 2.

¹⁵⁹² Compton WM, Lopez MF. Pathways to heroin use: Commentary on McCabe et al. *J Addict Med.* 2021;15(3):178-180, at pp. 178-179. Wilson Compton is the Deputy Director of the National Institute on Drug Abuse (NIDA), see <https://www.drugabuse.gov/about-nida/organization/offices/office-nida-director-od/biography-wilson-compton-md-mpe>

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- ii. Further, McCabe *et al* report that among their sample population already using heroin by age 18 (n=179), 22% used heroin following non-medical use of prescription opioids, and 39% used heroin and prescription opioids non-medically within the same year and 13% misused prescription opioids after initiating with heroin.¹⁵⁹³ The increased access and supply of prescription opioids has increased the risk of teenagers and young adults being exposed to any opioid. Prescription opioid use and heroin use are inextricably intertwined.
- g. Writing in the journal *Pediatrics* (2018) Harbaugh *et al.* report that “The majority of US high school seniors with both medical use and nonmedical use of prescription opioids reported medical use before initiating nonmedical use of prescription opioids, suggesting a role of leftover prescriptions in the transition to a nonmedical use of prescription opioids. This may be due, in part, to the perception that prescription opioids are safe if they are prescribed by physicians despite the fact that the addiction potential is similar to heroin.”¹⁵⁹⁴
- h. There is a clear causal link between prescription opioid exposure and the subsequent use of heroin and other illicit opioids.
 - i. The natural history of the disease of addiction is that individuals with addiction require increasing amounts and/or more potent forms over time to overcome tolerance, to maintain physiologic homeostasis, and to avoid painful withdrawal.
 - ii. Scientific literature supports the conclusion that greater exposure to prescription opioids is associated with greater transition to heroin. An authoritative CDC study concluded, “Frequent nonmedical users - people reporting 100-365 days of PYNMU [Per Year Nonmedical Use] - had the highest rate of past year heroin use and were at increased risk for ever injecting heroin (aOR 4.3, 95% CI 2.5-7.3) and past year heroin abuse or dependence (aOR 7.8, 95% CI 4.7-12.8) compared to infrequent nonmedical users (1-29 days of PYNMU).”¹⁵⁹⁵ Note that this study relied on NSDUH data, which investigated only nonmedical users of prescription opioids; therefore the study does not mean that medical users are somehow immune to the risk of transition to heroin. To the contrary, as demonstrated by McCabe, subjects who had only reported medical use of prescription opioids experienced a statistically significant, 2.68-fold increased risk of transition to heroin use.¹⁵⁹⁶

¹⁵⁹³ McCabe, “From Pills to Powder”, fn. 1589, above, at p. 3.

¹⁵⁹⁴ Harbaugh CM, Lee JS, Hu HM, *et al.* Persistent Opioid Use Among Pediatric Patients After Surgery. *Pediatrics*. 2018;141(1):e20172439, at p. 5.

¹⁵⁹⁵ Jones CM, Heroin use and heroin use risk behaviors among nonmedical users of prescription opioid pain relievers – United States, 2002-2004 and 2008-2010. *Drug Alcohol Depend.* 2013;132(1-2):95-100, at p. 95.

¹⁵⁹⁶ McCabe, “From Pills to Powder”, fn. 1589, above, at Table 2.

- iii. The finding of greater transition to heroin with more prescription opioid use provides an example of a dose-response relationship between exposure to a risk factor and the occurrence of an adverse outcome, and such a dose-response relationship is a hallmark of cause and effect. Further, the adjusted Odds Ratio (aOR) of 4.3, as reported in the CDC study, above, falls within the range of “strong” associations, another indicator of cause and effect between exposure to prescription opioids and the outcome of heroin abuse. *See* Section §C.13 of this Report for a detailed discussion of the factors considered in determining whether an association is likely to be causal.
- iv. As increasing numbers of Americans became addicted to prescription opioids over the past two decades, they were forced to seek out cheaper and more potent opioids. The illicit drug market met that increased demand with cheap and available heroin and fentanyl. Fentanyl, which is 50-100 times more potent than heroin and comes in white powder form similar to heroin, made its way into the illicit market without users realizing what they were ingesting, resulting in a surge of fentanyl related overdose deaths.¹⁵⁹⁷
- v. “A preponderance of evidence suggests that the major increase in prescription opioid use beginning in the late 1990s has served as a gateway to increased heroin use¹⁵⁹⁸...The interrelated nature of the prescription and illicit opioid epidemics means that one cannot be addressed separately from the other.”¹⁵⁹⁹
- vi. In the 1960s, 80% of opioid users reported that their first exposure to opioids was in the form of heroin. By the 2000s, however, 75% of opioid users reported that their first exposure to opioids was in the form of prescription painkillers.¹⁶⁰⁰
- vii. In a study based on NSDUH data from 2002-2011, the incidence of heroin use among people who reported prior nonmedical use of prescription opioids was 19 times as high as the incidence among persons who reported no previous nonmedical use.¹⁶⁰¹

¹⁵⁹⁷ “IMF [illicitly manufactured fentanyl] is most commonly mixed with or sold as white powder heroin.” Gladden RM, Martinez P, Seth P. Fentanyl Law Enforcement Submissions and Increases in Synthetic Opioid-Involved Overdose Deaths — 27 States, 2013–2014. *MMWR Morb Mortal Wkly Rep* 2016;65:837–843, at pp. 836, 840-841. DOI: [http://dx.doi.org/10.15585/mmwr.mm6533a2external icon](http://dx.doi.org/10.15585/mmwr.mm6533a2external%20icon).

¹⁵⁹⁸ NASEM Report (2017) at fn. 58, above at p. 215. *See also* discussion of Paulozzi (2006), *supra*, at §C.3.b.

¹⁵⁹⁹ *Id.* at p. 248.

¹⁶⁰⁰ Cicero TJ, Ellis MS, Surratt HL, Kurtz SP. The changing face of heroin use in the United States: A retrospective analysis of the past 50 years. *JAMA Psychiatry*. 2014. doi:10.1001/jamapsychiatry.2014.366, at p. E-1.

¹⁶⁰¹ Muhuri PK, Gfroerer JC, Davies MC. Associations of nonmedical pain reliever use and initiation of heroin use in the United States. *CBHSQ Data Rev.* 2013;(August):1-16, at p. 1.

- viii. Prescription opioid use disorder/addiction is associated with a likelihood of heroin addiction that is 40 times as great as the likelihood with no prescription-opioid misuse or addiction, even after accounting for sociodemographic, geographic, and other substance abuse or dependence characteristics.¹⁶⁰²
- ix. Eighty-six percent of urban people who used injected heroin in New York and Los Angeles in 2008 and 2009 had used prescription opioids nonmedically before using heroin.¹⁶⁰³ Similar studies conducted in San Diego, Seattle, and New York showed that 40%, 39%, and 70% of heroin users, respectively, reported that they had used prescription opioids nonmedically before initiating heroin use.¹⁶⁰⁴
- x. Muhuri found that 79.5% of persons who recently began using heroin had used prescription opioids nonmedically before initiating heroin use.¹⁶⁰⁵
- xi. A study of heroin users in Wilmington, Delaware, found that “most reported that prescription opioids were indeed their gateway to heroin use.”¹⁶⁰⁶
- xii. A 2014 research paper evaluating transitions from opioid pills to heroin injecting in Philadelphia and San Francisco, concluded that, “Unlike those substances previously labeled ‘gateway drugs’, opioid pills seem to have a direct relationship with progression to heroin initiation.”¹⁶⁰⁷
- xiii. A recent article by Pielech, *et al.*, stated, “Emerging data indicate that *any* exposure to opioids as an adolescent (medical or non-medical) appears to present short and long term risks for initiating heroin and prescription opioid use.”¹⁶⁰⁸

¹⁶⁰² Compton WM, Jones CM, Baldwin GT. Relationship between Nonmedical Prescription-Opioid Use and Heroin Use. *N Engl J Med*. 2016. doi:10.1056/NEJMr1508490, at p. 157.

¹⁶⁰³ Lankenau SE, Teti M, Silva K, Bloom JJ, Harocopos A, Treese M. Initiation into prescription opioid misuse amongst young injection drug users. *Int J Drug Policy*. 2012;23(1):37-44, at p. 41.

¹⁶⁰⁴ Compton, *et al.*, “Relationship Between NPOU and Heroin Use,” fn. 1602, above, at p. 156.

¹⁶⁰⁵ Muhuri, *et al.*, “Associations of NMPRU and Heroin,” fn. 1601, above, at p. 1.

¹⁶⁰⁶ Inciardi JA, *et al.*, Prescription Opioid Abuse and Diversion in an Urban Community: The Results of an Ultra-Rapid Assessment. *Pain Medicine*. 2009;10:537-548, at p. 544.

¹⁶⁰⁷ Mars SG, *et al.*, “Every ‘Never’ I Said Came True”: Transitions from Opioid Pills to Heroin Injecting. *Int’l J. of Drug Policy*. 2014;25:257-266, at p. 264

¹⁶⁰⁸ Pielech, *et al.*, Receipt of Multiple Outpatient Prescriptions Is Associated With Increased Risk of Adverse Outcomes in Youth: Opioid Prescribing Trends, Individual Characteristics, and Outcomes from 2005-2016. *PAIN* 2020, published ahead of print. DOI:10.1097/j.pain.0000000000001812, at p. 2 (emphasis in original).

- xiv. The number of Americans aged 12 and older with past month heroin use, rose from 281,000 to 335,000 between 2011 and 2013, a significant increase from the 166,000 using heroin in 2002.¹⁶⁰⁹
- xv. Jalal *et al.* (2018) also support the Gateway Effect, since those authors state: “Each drug’s mortality curve shows some variability. For example, the mortality rate from prescription opioids decreased slightly in 2012, whereas the mortality rates from heroin and synthetic opioids have been increasing rapidly. These trends may be related because several epidemic interventions may have reduced the impact of prescription opioids around 2010, including the reformulation of OxyContin in 2010, implementation of pain clinic laws and mandatory checking of Prescription Drug Monitoring Program data by prescribers, the reduction in the amount of opioids prescribed, and the rescheduling of hydrocodone compounds in 2014. Although these changes may have reduced the overdose deaths from prescription opioids, it is possible that they may have led some opioid-dependent persons to switch to illicit opioids such as heroin and fentanyl.”¹⁶¹⁰
- xvi. Another study put it this way: “The widespread availability of opioid analgesics outside sanctioned channels and, paradoxically, medical and regulatory attempts to curb this through monitoring and limiting prescribing, appear to be drawing a new generation into higher risk heroin injecting. Unlike those substances previously labeled ‘gateway drugs’, opioid pills seem to have a direct relationship with progression to heroin initiation.”¹⁶¹¹
- xvii. In 2017, more than 28,000 deaths in the United States involved a synthetic opioid, primarily fentanyl, more deaths than from any other type of opioid.¹⁶¹²
- i. The epidemic of prescription opioid misuse, addiction, and overdose death beginning in the 1990s has been a significant factor contributing to the subsequent increase in heroin and fentanyl misuse, addiction, and overdose death. Further, the Pharmaceutical Opioid Industry knew that prescription opioids are a gateway to illicit opioids. In March 2011, Purdue’s “Hair Testing

¹⁶⁰⁹ McCarthy M. Illicit drug use in the US holds steady, but heroin use is on rise. *BMJ*. 2013;347(September):f5544. doi:10.1136/bmj.f5544, at p. 1.

¹⁶¹⁰ Jalal H, Buchanich JM, Roberts MS, Balmert LC, Zhang K, Burke DS. Changing dynamics of the drug overdose epidemic in the United States from 1979 through 2016. *Science*. 2018. doi:10.1126/science.aau1184, at pp. 1-2. (internal citations omitted)

¹⁶¹¹ Mars SG, Bourgois P, Karandinos G, Montero F, Ciccarone D. “Every ‘Never’ I Ever Said Came True”: Transitions from opioid pills to heroin injecting. *Int J Drug Policy*. 2014;25(2):257-266. doi:https://doi.org/10.1016/j.drugpo.2013.10.004, at p. 264.

¹⁶¹² Centers for Disease Control and Prevention. *Synthetic Opioid Overdose Data*, (Apr. 2, 2019) <https://www.cdc.gov/drugoverdose/data/fentanyl.html>.

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Advisory Panel,” convened to help make the argument in favor of OxyContin’s “tamper-resistant formulation,” concluded that one of the “anticipated impacts of reformulation” was “reducing *OxyContin’s role as a gateway drug*” for recreational users.¹⁶¹³

- j. A lengthy and authoritative report issued in February 2022 by the U.S. Commission on Combatting Synthetic Opioid Trafficking included the following significant conclusion: “The rise in illicit fentanyl and other synthetic opioid misuse and related deaths has its origins in the U.S. Food and Drug Administration’s approval of the prescription opioid painkiller OxyContin in 1995. Since then, the number of fatal drug overdoses has steadily climbed. *OxyContin and other prescription opioids were falsely marketed as an easy, nonaddictive fix for pain* without an appreciation of a patient’s other conditions, such as depression, trauma, and anxiety, which could drive the drugs’ misuse. *Prescription opioid dependence and addiction increased dramatically in the United States, and traffickers and other criminals exploited the opportunities presented.*”¹⁶¹⁴
- k. Increased access/exposure to prescription opioids contributed not only to increased heroin and illicit fentanyl death; it also contributed to increased non-opioid overdose deaths, including sedatives and stimulants. A 2020 study by Segel *et al.*, in examining the relationship between state-level opioid overdose death rates at the beginning of the opioid epidemic (1999-2004) and overdose death rates for opioids and other substances in later years (2005-2018), found the following: “our results suggest two characteristics of the opioid crisis: persistence and pervasiveness. In adjusted analysis, we found that for each additional opioid overdose death per 100,000 population at baseline, states had 23.5 more opioid deaths, 4.4 more heroin deaths, 8.0 more synthetic opioid deaths, 9.2 more sedative deaths, 3.3 more stimulant deaths, and 4.6 more cocaine deaths per population from 2005 to 2018.”¹⁶¹⁵ In sum, “After adjusting for sociodemographic and state-level differences, baseline opioid overdose death rates in 1999-2004 were significantly associated with future opioid- and non-opioid-related overdose death rates.”¹⁶¹⁶ The association reported by Segel *et al.* is likely to be causal because of the known phenomena of reinstatement (relapse) and cross-addiction, wherein patients addicted to prescription opioids are more susceptible to addiction to other drugs, especially when their drug of choice is not available.

¹⁶¹³ PPLP003370086 at 0106 (emphasis added).

¹⁶¹⁴ United States of America Commission on Combating Synthetic Opioid Trafficking: Final Report. (Feb. 8, 2022) https://www.rand.org/pubs/external_publications/EP68838.html, at p. ix (emphasis added)

¹⁶¹⁵ Segel JE, *et al.* Persistence and Pervasiveness: Early wave opioid overdose death rates associated with subsequent overdose death rates. *Public Health Reports*. 2020;00(0):1-7, at p. 1.

¹⁶¹⁶ *Id.* at p. 3.

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- i. Neuroscientists have shown that brain changes that occur after continuous heavy use of addictive substances can cause damage that does not resolve even after years of abstinence. One of the ways these irreversible changes can manifest is that the brain is primed to relapse to addictive physiology even after a single exposure to the addictive substance.¹⁶¹⁷ This is called “reinstatement” by neurobiologists, and “relapse” by those who are addicted.
- ii. Reinstatement is not triggered solely by the substance that the individual was previously addicted to. Reinstatement can occur with any addictive substance because all drugs of abuse work on the same brain reward pathway.¹⁶¹⁸ For example, animals repeatedly exposed to the addictive component of marijuana (tetrahydrocannabinol, or THC) and then not given THC for a period of time become addicted to morphine more quickly than animals not previously exposed to THC.¹⁶¹⁹ This phenomenon is called cross-sensitization, or cross-addiction. Individuals who are addicted to opioids are consequently more susceptible to addiction to other drugs, including sedatives and stimulants.
- iii. I have written and published peer-reviewed literature describing the Gateway Effect on two occasions prior to my becoming an expert witness in the Opioid Litigation. In my 2016 book, *Drug Dealer MD*, I included a chapter with the title, “Prescription Drugs as the New Gateway to Addiction,” including a subchapter, “Vicodin: A Gateway Drug,” which recounted the example of a patient who transitioned from Vicodin to heroin after receiving the prescription hydrocodone drug for wisdom teeth removal. Similarly, in an article submitted for publication in 2017, and ultimately published in February 2018, I wrote: “Overprescribing of benzodiazepines may be fueling the use of illicit analogues, just as overprescribing of opioids has fueled increases in heroin and illicit fentanyl use.” These statements are consistent with the consensus in the field, that prescription opioids do indeed lead to transition to illicit opioids

10. Increased supply of prescription opioids contributed substantially to more individuals, including newborns, becoming dependent on opioids, increasing their risk for opioid-related morbidity and mortality (The Dependence Effect).

¹⁶¹⁷ Steketee JD, Kalivas PW. Drug Wanting: Behavioral sensitization and relapse to drug-seeking behavior. *Pharmacol Rev.* 2011;63:348-365.

¹⁶¹⁸ Nestler EJ, Is there a common molecular pathway for addiction? *Nature Neuroscience.* 2005;8(11):1445-1449.

¹⁶¹⁹ Cadoni C, *et al.* Behavioral sensitization after repeated exposure to Δ9-tetrahydrocannabinol and cross-sensitization with morphine. *Psychopharmacology.* 2001;158:259-266, at p. 266.

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- a. Prescription opioids induce physiological dependence almost universally, and dependence leads to addiction in a significant subset of users, particularly as dose and duration of exposure are increased.
- b. Over the last 30 years, the liberal prescribing of opioids for chronic pain has created a “legacy” population of patients who have been on opioids for several years if not decades, and are now physically dependent on opioids, making it difficult to come off (The Dependence Effect).
- c. Physiologic dependence, as currently defined by the DSM-5, is not the same as addiction. Dependence is the process whereby the body comes to rely on the drug to maintain biochemical equilibrium. When the drug is not available at expected doses or time intervals, the body becomes biochemically dysregulated, which manifests as the signs and symptoms of withdrawal. Although opioid dependence as currently defined is not the same as addiction, dependence on opioids can be associated with significant morbidity and mortality, and thus is not the same thing as dependence on other medications used as evidence-based treatment for illness.¹⁶²⁰ Also, while dependence is defined differently from addiction, the line between them is not well-defined; in particular, the evidence of addiction often comes when an opioid-dependent patient attempts to taper and discovers that the loss of the drug causes the craving and compulsion that define addiction. In my clinical experience, dependence in some individuals can develop quickly. This clinical experience is consistent with studies showing that even short-term prescriptions of opioids for acute injuries result in long-term use of opioids after the acute condition has passed.¹⁶²¹ In the DSM-4, the edition prior to the DSM-5, “opioid use disorder” was called “opioid dependence.” The new DSM-5 criteria made it more difficult to diagnose Opioid Use Disorder (opioid addiction), by removing the criteria of withdrawal, and tolerance from the definition in the case of a patient taking prescribed opioids under a doctor’s care. The DSM-5 thereby reduced the proportion of patients who could be diagnosed with opioid use disorder.
- d. By 2005, long-term opioid therapy was being prescribed to approximately 10 million Americans. “In 2014 alone, U.S. retail pharmacies dispensed 245 million prescriptions for opioid pain relievers. Of these prescriptions, 65% were for short-term therapy (<3 weeks), but 3 to 4% of the adult population (9.6 million to 11.5 million persons) were prescribed longer-term opioid therapy.”¹⁶²²

¹⁶²⁰ Lembke, *et al.*, “Weighing the Risks,” fn. 5, above.

¹⁶²¹ Delgado M, *et al.* National Variation in Opioid Prescribing and Risk of Prolonged Use for Opioid-Naive Patients Treated in the Emergency Department for Ankle Sprains. *Ann Emerg Med.* 2018, at p. 1; *see also* Howard R, Fry B, Gunaseelan V, *et al.* Association of Opioid Prescribing with Opioid Consumption after Surgery in Michigan. *JAMA Surgery.* 2018, at p. E-6.

¹⁶²² Volkow, *et al.*, “Misconceptions and Mitigation,” fn. 50, above, at p. 1253.

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- e. Once established, opioid dependence represents a complex, debilitating, and sometime irreversible clinical problem. In some cases, the suffering from withdrawal is so extreme that patients say they would rather die than go through it. Indeed, people can die from opioid withdrawal, due to vital sign instability, suicide, and other complications.
- f. Opioids cause neuroadaptation¹⁶²³ and lead to tolerance, physiologic dependence, and painful withdrawal, even without the more complex biopsychosocial disease of addiction. As such, tolerance, dependence, and withdrawal in and of themselves represent real harm to patients as a result of opioid therapy. Due to tolerance, dependence, and withdrawal, many patients taking prescription opioids today will require an enormous investment of resources to help them get off of opioids or onto lower, safer doses.
- g. Withdrawal refers to the physiologic manifestations of not having the substance, the symptoms of which vary from substance to substance. As a general albeit oversimplified principle, the characteristics of withdrawal from a given substance are the opposite of intoxication for that substance. Withdrawal from opioids includes dysphoria (unhappiness), anxiety, insomnia, agitation, restlessness, muscle fasciculations, increased heart rate, elevated blood pressure, diarrhea, nausea, vomiting, and body pain. Although opioid withdrawal is generally thought to be painful but not life threatening, people can die from opioid withdrawal, due to vital sign instability, suicide, and other complications.¹⁶²⁴
- h. Clinical experience and clinical studies demonstrate that the majority of opioid legacy chronic pain patients (that is, patients who have been taking opioids daily for months to years) are physiologically dependent on opioids and struggle to taper, even when opioids pose imminent risk.
- i. In a study at Oregon Health & Sciences University, after a hospital and clinic wide policy was implemented to get high dose legacy patients' doses down below 120 MED per day, including intensive physician education from 2011 to 2013,¹⁶²⁵ 71 (63%) continued high-dose opioids in the post-intervention period.¹⁶²⁶ In other words, even with a hospital wide initiative, a minority of patients tapered to safer doses.

¹⁶²³ Koob, "Neurocircuitry", fn. 46, above, at p. 217.

¹⁶²⁴ Stark MM, Payne-James J. People can die from opiate withdrawal. *Med Sci Law*. 2017;57(2):103. doi:10.1177/0025802417704600 at p. 103; *see also* Bohnert ASB, Valenstein M, Bair MJ, *et al.* Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA - J Am Med Assoc*. 2011;305(13):1315-1321, at p. 77.

¹⁶²⁵ Weimer MB, Hartung DM, Ahmed S, Nicolaidis C. A chronic opioid therapy dose reduction policy in primary care. *Subst Abus*. 2016;37(1):141-147, at pp. 141-142.

¹⁶²⁶ *Id.* at p. 114.

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- ii. In a Danish study in which subjects were tapered off of opioids by reducing by 10% of the daily opioid dose every week until discontinuation,¹⁶²⁷ only 13 of 35 patients randomized to the opioid taper completed the study without dropping out. The authors wrote “Although our study is hampered by a vast dropout rate, we still feel that it is highly justified to point to the fact that the stabilization of opioid treatment is not a simple task and opioid tapering off seems to be extremely difficult in CNCP patients in general”¹⁶²⁸
- i. The Pharmaceutical Opioid Industry consistently sought to downplay the importance of “dependence” on prescription opioids. As explained below, this effort included influencing the American Psychiatric Association’s change of the definitions of opioid-related disorders from the Diagnostic and Statistical Manual (DSM) IV to the DSM-5.
- j. On May 18, 2006, Purdue’s David Haddox received the “excellent news” from Sidney Scholl of Pinney Associates that “Chuck O’Brien will be heading up the SUD [Substance Use Disorder] section of the DSM-V. This means that there is a good chance that ‘addiction’ will replace ‘dependence’ and there can be some changes in the diagnostic criteria that will reflect issues related to abuse and addiction of prescription opioids. Chuck asked me to assist him in this process. I would appreciate your input in this process. . . . If Marc Schuckit, who was originally slated to head up the SUD section, was still in charge, we would not be in this position as he likes the use of dependence over addiction. This is an opportunity we should not overlook, as major revisions of the DSM do not occur very often.” Haddox wrote back, “This is really good news, Sid.”¹⁶²⁹
- k. On March 24, 2008, Haddox wrote to Phillipp Lippe in response to Lippe’s request for comments regarding the American Medical Association’s Report on Substance Abuse. Haddox wrote, “I am glad to see AMA getting into this area. Certainly the definitions and diagnostic criteria need some work. . . . we are all fortunate that Charles O’Brien is the head of the substance use disorders section.”¹⁶³⁰
- l. On November 6, 2008, Haddox wrote to Chuck O’Brien, “It was good to see you this past weekend at ICPCD [International Conference on Pain and Chemical Dependency]. I really am excited that you are educating your nonclinical colleagues about the need for diagnostic nomenclature that are applicable in the real (read: clinical) world.” Haddox went on to ask O’Brien to consult on a tamper-resistant opioid analgesic work group, and referenced prior payment of \$2400 at O’Brien’s rate of \$600 per hour, “when it was anticipated

¹⁶²⁷ Kurita GP, Højsted J, Sjøgren P. Tapering off long-term opioid therapy in chronic non-cancer pain patients: A randomized clinical trial. *Eur J Pain*. 2018;22(8):1528-1543, at p. 1531.

¹⁶²⁸ *Id.* at p. 1536.

¹⁶²⁹ PPLP004058443.

¹⁶³⁰ PPLPC031000425439.

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that you would accompany us to the FDA Advisory Committee in March.” Haddox added, “Also, in the interest of public health and medicine, I don’t want to do anything to impair your ability to complete your DSM-V duties.” O’Brien wrote back on November 12, 2008, to “Dave, I would be very happy to do this but it would simplify my life with Penn if we could consider this activity an extension [of] my efforts of several months ago where I already signed a contract.” Haddox replied that he was “really pleased that you will be able to work with us on this.”¹⁶³¹

- m. On March 25, 2008, Haddox again exchanged emails with Phillipp Lippe. Dr. Lippe expressed concern that under DSM-IV, the first three criteria for diagnosis of substance dependence “are inherent in pain management,” that is, “(1) Tolerance; (2) withdrawal symptoms; and (3) increased dosage or length of use.” Haddox wrote to Lippe, “I have great confidence that the DSM-V will improve on this language, based on the chair of the SUD [committee].”¹⁶³²
- n. Dr. O’Brien’s consulting and financial relationship with Purdue goes back to at least 2003.¹⁶³³ Through 2006, Dr. O’Brien appeared as an expert witness for Purdue in at least 9 cases in the federal courts of Florida, Missouri, Ohio, Texas, Georgia and Illinois and Texas state court¹⁶³⁴ providing opinions that plaintiffs were not addicted; not injured by dependence, which was described as an “expected consequence” of taking OxyContin and easily resolved by tapering.¹⁶³⁵ In the Savant v. Purdue case in 2005, Dr. O’Brien’s report stated that he was compensated at the rate of \$550 per hour.¹⁶³⁶ O’Brien signed a consulting agreement with Purdue, effective from April 2008-April 2013,¹⁶³⁷ essentially contemporaneous with his tenure as Chair of the DSM-5 Substance

¹⁶³¹ PPLPC018000252189 at -2190-2191.

¹⁶³² PPLPC018000201219 at -1219-1222.

¹⁶³³ Dr. O’Brien testified that since 1969, he has been a paid consultant to numerous pharmaceutical/opioid manufacturers including McNeil, Janssen, Johnson & Johnson, Cephalon, Purdue and others. O’Brien also testified that he “helped them [McNeil] decide to purchase Tramadol from a German company and help them get that started.” *Timmons v Purdue Pharma* (2005) Deposition of Charles P. O’Brien, produced at PKY183320282 at -0393-0394.

¹⁶³⁴ *Timmons v Purdue Pharma et al.* No. 8:04-CV-1479-T-26MAP (M.D. Fla., 2005) produced at PKY183320282; *Savant v Purdue Pharma et al.*, No. 04-394-DRH, 2005 WL 6503987 (S.D. Ill. 2005); *Taylor v Purdue Pharma et al.*, No. 504-CV-197, 2005 WL 3308504 (M.D. Ga. 2005); *McKnight v Purdue Pharma et al.*, No. 9:04 Civ-116, 2005 WL 5794391 (E.D. Tex. 2005); *Harris v Purdue Pharma et al.*, No. C-1-01-428, 2004 WL 4012101 (S.D. Ohio 2004); *Branch v Purdue Pharma et al.* No. LR 1696-3, 2004 WL 3752789 (Tex. Dist. Richmond Civil); *Campbell v Purdue Pharma et al.*, No. 1:02CV00163TCM, 2004 WL 6057307 (E.D. Mo. 2004); *Labzda v Purdue Pharma et al.*, No. 01-8726-CIV-FERGUSONSNOW, 2003 WL 26100920 (S.D. Fla. 2003); *Williams v Purdue Pharma et al.*, No. 4:04CV02407 (S.D. Tex. 2006), produced at PKY182921037

¹⁶³⁵ *Harris*, 2004 WL 4012101, at *5.

¹⁶³⁶ *Savant*, 2005 WL 6503987, at *9.

¹⁶³⁷ PPLP003478540

Abuse working group, from 2007-2013.¹⁶³⁸ Remarkably, in 2013, O'Brien disclosed no financial relationship to Purdue or any other party as a co-author and Chair of the group that published the rationale for the changes to the new DSM-5 section on substance abuse.¹⁶³⁹

- o. This sequence of events indicates that Purdue's consultant, O'Brien, who was on a first name basis with Haddox, was responsible for the work that altered the DSM-5 definition of opioid use disorder in a manner that suited Purdue's goals by distinguishing between "dependence" on the one hand, and "use disorder" or "addiction" on the other. This history is consistent with a larger effort on the part of Purdue and other opioid manufacturers to characterize dependence as a benign condition entirely separate from addiction. In reality, dependence, withdrawal, and tolerance, are closely linked to the disease of addiction, and from a neurobiological perspective, may be identical phenomena. Further, by excluding the criteria of tolerance and withdrawal, and by completely removing dependence from the diagnostic criteria, the DSM-5 raised the threshold for diagnosing OUD in this vulnerable population, consisting of approximately 25% of long-term opioid users who progressed to OUD.¹⁶⁴⁰ As a result of making it more difficult to diagnose OUD, some of these patients were denied the benefits of timely, evidence-based treatment of their conditions.
- p. Regardless of these changing and disparate definitions, the bottom line has not changed: prescription opioids induce physiological dependence almost universally, and result in addiction in a significant subset of users, particularly as dose and duration of exposure are increased. Both represent significant harms.
- q. Even limited exposure to opioids through a doctor's prescription, can lead to persistent opioid use. In other words, once patients start opioids, they are at significant risk to continue them beyond the time of injury, *i.e.* to become dependent on them.
 - i. Brummett *et al.* sought to determine the incidence of new persistent opioid use after minor and major surgical procedures. Using a nationwide insurance claims data set from 2013 to 2014, they calculated the incidence of persistent opioid use for more than 90 days among opioid-naïve patients after both minor and major surgical procedures. The authors found the rates of new persistent opioid use were similar between the two groups, ranging from 5.9% to 6.5%. By

¹⁶³⁸ Hasin DS, O'Brien CP *et al.* DSM-5 Criteria for Substance Use Disorders: recommendations and rationale. *Am J Psychiatry* 2013;170(8):834-851. at p.2, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3767415/pdf/nihms515995.pdf>, at p. 2.

¹⁶³⁹ *Id.* at pp. 1 and 12.

¹⁶⁴⁰ Vowles, "Rates of Opioid Misuse", fn. 1381, above, discussed above at §C.8.b.

comparison, the incidence in the nonoperative control cohort was only 0.4%. The authors wrote, “New persistent opioid use represents a common but previously underappreciated surgical complication that warrants increased awareness.”¹⁶⁴¹ The more opioids prescribed after surgery, the more patients tend to use. The number of opioid pain pills prescribed after surgery is a bigger predictor of how many opioids the patient will use, than is self-reported pain.

- ii. A study by Delgado *et al.* looked at opioid naïve patients being treated for a common minor injury, ankle sprain, in the emergency department (ED) to determine the association between initial opioid prescription intensity and transition to prolonged opioid use. The authors concluded that opioid prescribing for ED patients treated for ankle sprains is “common,” and prescriptions greater than 225 MED were associated with approximately five times higher rates of prolonged opioid use than with lower MED exposure. As the authors stated, “This is concerning because these prescriptions could still fall within 5- or 7-day supply limit policies aimed at promoting safer opioid prescribing.”¹⁶⁴²
- iii. A 2020 retrospective cohort study of 259,115 opioid naïve adult patients undergoing endocrine surgery found the rate of new persistent opioid use [*i.e.*, receipt of 1 or more opioid prescriptions 90-180 days postop with no intervening procedures] was 7.4% but that “[i]mportantly, the risk for persistent opioid use increased with higher doses of total amount of opioids prescribed.”¹⁶⁴³
- iv. A 2022 study mentioned previously found 29.9% of patients transitioned from acute opioid use to chronic opioid use. Risk factors included higher MME, higher tablet count and longer prescription duration in the initial opioid prescription.¹⁶⁴⁴ The study demonstrated a “dose-dependent relationship between [the number of] tablets prescribed and chronic opioid use risk.”¹⁶⁴⁵ These findings support my experience that the more times per day people can dose themselves, especially with short-acting opioids, the more likely they are to develop opioid use disorder.

¹⁶⁴¹ Brummett CM, Waljee JF, Goesling J, *et al.* New persistent opioid use after minor and major surgical procedures in U.S. adults. *JAMA Surg.* 2017., at p. 1.

¹⁶⁴² Delgado, *et al.*, “National Variation,” fn. 1621, above, at p. 1

¹⁶⁴³ Kuo JH, *et al.* Use and Misuse of Opioids after Endocrine Surgery Operations. *Annals of Surgery.* 2020:1-6, at p. 1.

¹⁶⁴⁴ Johnson, “Prescription quantity and duration”, fn. 1464, above, at p. 1.

¹⁶⁴⁵ *Id.*, at p. 10.

- v. Numerous other studies have been published showing persistent opioid use 3-12 months after even minor surgeries in opioid naïve patients: (10%¹⁶⁴⁶; 10%¹⁶⁴⁷; 5%¹⁶⁴⁸; 13%¹⁶⁴⁹; 13%¹⁶⁵⁰; 8%¹⁶⁵¹; 10%-13%¹⁶⁵²)
- r. Conversely, the fewer opioids prescribed in the weeks and months following surgery, the less likely patients are to become persistent opioid users.¹⁶⁵³ When opioids are restricted, patients do not tend to experience more pain, less satisfaction, or call in more frequently for refills.¹⁶⁵⁴
- s. A 2020 NASEM Report addresses the role of opioid prescribing for acute pain, including surgical and other contexts, as a contributing factor to the epidemic of abuse, overdose and mortality.¹⁶⁵⁵ The Report confirms the increasing awareness that opioids are overprescribed even for acute pain, and that an important subset of acute pain patients go on to long-term use of prescription opioids and the risks that accompany such use.¹⁶⁵⁶

¹⁶⁴⁶ Marcusa DP *et al.* Prescription Opioid Abuse among Opioid-Naïve Women Undergoing Immediate Breast Reconstruction. *Plast Reconstr Surg.* 2017 Dec;140(6):1081-1090. doi: 10.1097/PRS.0000000000003832, at p. 1081.

¹⁶⁴⁷ Lee JS *et al.* New Persistent Opioid Use Among Patients with Cancer after Curative-Intent Surgery. *J Clin Oncol.* 2017 Dec 20;35(36):4042-4049. doi: 10.1200/JCO.2017.74.1363, at p. 4042.

¹⁶⁴⁸ Harbaugh, *et al.*, “Persistent Opioid Use”, fn. 1594, above, at p. 1.

¹⁶⁴⁹ Deyo RA *et al.* Use of Prescription Opioids Before and After an Operation for Chronic Pain (lumber fusion surgery). *Pain.* 2018 Jun;159(6):1147-1154. doi: 10.1097/j.pain.0000000000001202, at p. 5.

¹⁶⁵⁰ Johnson SP *et al.* Risk of Prolonged Opioid Use Among Opioid-Naïve Patients Following Common Hand Surgery Procedures. *J Hand Surg Am.* 2016 Oct;41(10):947-957.e3. doi: 10.1016/j.jhsa.2016.07.113, at p. 947.

¹⁶⁵¹ Goesling J *et al.* Trends and Predictors of Opioid Use After Total Knee and Total Hip Arthroplasty. *Pain.* 2016 Jun;157(6):1259-65. doi: 10.1097/j.pain.0000000000000516, at p. 1259.

¹⁶⁵² Cook DJ *et al.* Benchmarks of Duration and Magnitude of Opioid Consumption After Total Hip and Knee Arthroplasty: a database analysis of 69,368 patients. *J. Arthroplasty.* 2019; 34: 638-644, at p. 638.

¹⁶⁵³ Brummett, “New Persistent Opioid Use”, fn. 1641, above; Gil JA, *et al.* Risk of Prolonged Opioid Use Among Opioid-Naïve Patients After Common Shoulder Arthroscopy Procedures. *Am J Sports Med* 2019; 47(5): 1043-1050, at p. 1049; Larach DB, Sahara MJ, *et al.* Patient Factors Associated with Opioid Consumption in the Month Following Major Surgery. *Ann Surg.* 2019; 1-9, at p. 1.

¹⁶⁵⁴ Bateman BT, Cole NM, *et al.* Patterns of opioid prescription and use after cesarean delivery. *Obstet Gyn.* 2017; 130(1): 1-17, at p. 3; Howard R, *et al.* Reduction in opioid prescribing through evidence-based prescribing guidelines. *JAMA Surg* 2018; 153(3): 285-287, at p. 287; Lee JS, Hu HM, Brummett CM, *et al.* Postoperative Opioid Prescribing and the Pain Scores on Hospital Consumer Assessment of Healthcare Providers and Systems Survey. *JAMA.* 2017;317(19):2013–2015, at p. 2014; Sekhri S, Arora NS, *et al.* Probability of opioid prescription refilling after surgery: does initial prescription dose matter? *Ann Surg.* 2018; 268(2): 271-276, at p. 275.

¹⁶⁵⁵ National Academies of Sciences, Engineering, and Medicine (NASEM 2020). 2020. *Framing Opioid Prescribing Guidelines for Acute Pain: Developing the Evidence.* Washington, DC: The National Academies Press. <https://www.nap.edu/catalog/25555/framing-opioid-prescribing-guidelines-for-acute-pain-developing-the-evidence>

¹⁶⁵⁶ *Id.* at p. 1. A further recent publication adds to this evidence: among women who took prescription opioids for acute pain after childbirth, there was an increased risk of Serious Opioid-Related Events (a composite consisting of persistent opioid use, opioid use disorder diagnosis, methadone or buprenorphine prescription, opioid overdose diagnosis, and opioid-related death) compared with women who did not take opioids after childbirth, and the risk increased with more post-partum opioid prescriptions. Osmundson SS, *et al.*, Opioid prescribing after childbirth and

- t. Just as increased exposure has been the cause of increased consumption and risk,¹⁶⁵⁷ decreasing exposure decreases opioid consumption and risk. When doctors initiate fewer opioids, patients consume fewer opioids, without increases in pain. Limiting opioid prescribing is good medicine, because it decreases exposure to a dangerous and potentially lethal drug, without compromising pain treatment, while at the same time reducing the risk of diversion of unused pills to unauthorized users. Recent studies in a wide range of medical conditions have consistently demonstrated that patients' experience of pain is not increased when opioids are reduced or eliminated from treatment protocols. Examples of research are summarized below.
 - i. In a study in which patients were treated with Tylenol/ibuprofen after parathyroid and thyroid surgery, the authors concluded that such patients "need very little, if any, post-operative opioids....Decreasing the volume of opioid medications prescribed at discharge will decrease waste and reduce potential for addiction."¹⁶⁵⁸
 - ii. A case-control cohort study of 1,231 patients undergoing gynecologic oncology surgery, implemented an "ultrarestrictive opioid prescription protocol" (UROPP), resulting in a significant decrease in the number of opioids dispensed during the entire perioperative period, without changes in postoperative pain scores, complications, or increases in the number of refill requests.¹⁶⁵⁹
 - iii. The authors write, "For patients who underwent laparoscopic or robotic surgery, the mean (SD standard deviation) number of opioid tablets given at discharge was 38.4 (17.4) before implementation of the UROPP and 1.3 (3.7) after implementation ($P < .001$). After ambulatory surgery, the mean (SD) number of opioid tablets given at discharge was 13.9 (16.6) before implementation of the UROPP and 0.2 (2.1) after implementation ($P < .001$). The mean (SD) perioperative oral morphine equivalent dose was reduced to 64.3 (207.2) mg from 339.4 (674.4) mg the year prior for all opioid-naïve patients ($P < .001$)."¹⁶⁶⁰
 - iv. "The significant reduction in the number of dispensed opioids was not associated with an increase in the number of refill requests (104

risk for serious opioid-related events: a cohort study. *Annals of Internal Medicine* 2020; doi:107326/M19-3805, at p. 2.

¹⁶⁵⁷ Howard, *et al.*, "Association of Opioid Prescribing," fn. 1621, above, at p. E6.

¹⁶⁵⁸ Shindo M, Lim J, Leon E, Moneta L, Li R, Quintinalla-Diek L. Opioid Prescribing Practice and Needs in Thyroid and Parathyroid Surgery. *JAMA Otolaryngology - Head and Neck Surgery*. 2018, at p. 1102.

¹⁶⁵⁹ Mark J, Argentieri DM, Gutierrez CA, *et al.* Ultrarestrictive Opioid Prescription Protocol for Pain Management After Gynecologic and Abdominal Surgery. *JAMA Netw Open*. 2018;1(8):e185452. doi:10.1001/jamanetworkopen.2018.5452.

¹⁶⁶⁰ *Id.* at p. 1.

patients [16.6%] in the pre-UROPP group vs 100 patients [16.5%] in the post-UROPP group; $P = .99$), the mean (SD) postoperative visit pain scores (1.1 [2.2] for the post-UROPP group vs 1.4 [2.3] for pre-UROPP group; $P = .06$), or the number of complications (29 cases [4.8%] in the post-UROPP group vs 42 cases [6.7%] in the pre-UROPP group; $P = .15$).¹⁶⁶¹

- v. Similarly, non-opioids have been found equivalent to opioids for relief of pain treated in emergency departments. “For adult ED [Emergency Department] patients with acute extremity pain, there were no clinically important differences in pain reduction at 2 hours with ibuprofen and acetaminophen or 3 different opioid and acetaminophen combination analgesics.”¹⁶⁶² Based on data from 2006-2010, opioids were prescribed for 18.7% of ED discharges; yet “[t]he findings support the inference that there are no clinically meaningful differences between the analgesic effects of these 4 analgesics and suggest that a combination of ibuprofen and acetaminophen represents an alternative to oral opioid analgesics for the treatment of acute extremity pain in the ED.”¹⁶⁶³
- vi. A 2024 international study of patients undergoing common acute and elective surgical procedures across 25 countries found that, after adjusting for confounders, opioid analgesia on discharge correlated with increased pain severity and complaints of medication side-effects when compared with opioid-free analgesia.¹⁶⁶⁴ The authors note that “It is becoming increasingly apparent across a range of surgical procedures that most patients do not benefit from opioid pain relief at discharge.”¹⁶⁶⁵
- u. In most cases, opioid dependent patients require a protracted medically supervised taper to lower their doses. I have worked with others to develop a protocol for safely and compassionately tapering opioid-dependent patients to lower doses or to eliminate them entirely. *See* discussion of the “BRAVO Protocol” and my recent publication on patient-centered tapering, below. Studies show that pain in the majority of patents *improves* when patients on chronic high dose opioid therapy reduce their dose or come off of opioids.

¹⁶⁶¹ *Id.* at pp. 1-2.

¹⁶⁶² Chang AK, *et al.* Effect of a Single Dose of Oral Opioid and Nonopioid Analgesics on Acute Extremity Pain in the Emergency Department: A Randomized Clinical Trial. *JAMA*. 2017;318(17):1661–1667. doi:10.1001/jama.2017.16190, at p.1661.

¹⁶⁶³ *Id.*

¹⁶⁶⁴ TASMAN Collaborative. Impact of opioid-free analgesia on pain severity and patient satisfaction after discharge from surgery: Multispecialty, prospective cohort study in 25 countries. *BJS*. 2024;111(1):1-9.

¹⁶⁶⁵ *Id.* at p. 7.

- v. It is inhumane to abruptly discontinue opioids in patients who have become dependent through a medical prescription.¹⁶⁶⁶ The preferred approach is a slow and compassionate taper¹⁶⁶⁷ when risks outweigh the benefits.
- w. A retrospective research study of patients consecutively admitted to the Mayo Clinic Pain Rehabilitation Center from 2006 through 2012, with a pain diagnosis of fibromyalgia, showed that patients tapered off of opioids had significant improvements in pain-related measures including numeric pain scores and functionality.¹⁶⁶⁸
- x. A meta-analysis of opioid legacy patients (patients on long-term opioid therapy as a “legacy” of opioid prescribing in the 1990s) demonstrated that pain improves for many patients who decrease or go off of long-term opioid therapy (LTOT). Sixty-seven studies were included in this analysis. Among 40 studies examining patient outcomes after dose reduction, improvement was reported in pain severity (8 of 8 fair-quality studies), function (5 of 5 fair-quality studies), and quality of life (3 of 3 fair-quality studies).¹⁶⁶⁹ The authors repeatedly note the need for more research and better quality evidence. Nonetheless, the authors concluded, “this systematic review suggests that pain, function and quality of life may improve during and after opioid dose reduction.”¹⁶⁷⁰
- y. In a study by Sullivan *et al.*, high dose legacy patients were randomly assigned to a 22-week taper support intervention (psychiatric consultation, opioid dose tapering, and 18 weekly meetings with a physician assistant to explore motivation for tapering and learn pain self-management skills) or usual care (N=35).¹⁶⁷¹ The authors write, “It is important to note that the opioid dose reduction in both the taper support and usual care groups was achieved without a significant increase in pain severity. In fact, pain severity decreased on average from baseline to 22 weeks by approximately 1 point on the 0-10 scale in the taper support group and approximately a half-point in the usual care group. This finding is consistent with those in studies of inpatient pain

¹⁶⁶⁶ United States Department of Health and Human Services. *HHS Guide for Clinicians on the Appropriate Dosage Reduction or Discontinuation of Long-term Opioid Analgesics*. (Oct. 2019);

https://www.hhs.gov/opioids/sites/default/files/2019-10/Dosage_Reduction_Discontinuation.pdf.

¹⁶⁶⁷ *Id.* at p. 3, opioid tapering flowchart based on Oregon Pain Guidance BRAVO protocol.

¹⁶⁶⁸ Cunningham JL, Evans MM, King SM, Gehin JM, Loukianova LL. Opioid tapering in fibromyalgia patients: Experience from an interdisciplinary pain rehabilitation program. *Pain Med* (United States). 2016. doi:10.1093/pm/pnv079, at p. 1676.

¹⁶⁶⁹ Frank JW, Lovejoy TI, Becker WC, *et al.* Patient outcomes in dose reduction or discontinuation of long-term opioid therapy: A systematic review. *Ann Intern Med*. 2017;167(3):181-191. doi:10.7326/M17-0598, at pp. 185-186.

¹⁶⁷⁰ *Id.* at p. 186.

¹⁶⁷¹ Sullivan MD, Turner JA, DiLodovico C, D’Appollonio A, Stephens K, Chan Y-F. Prescription Opioid Taper Support for Outpatients With Chronic Pain: A Randomized Controlled Trial. *J Pain*. 2017. doi:10.1016/j.jpain.2016.11.003, at p. 308.

rehabilitation programs, which have documented pain reduction with opioid dose reduction.”¹⁶⁷²

- z. A small outpatient study of opioid tapering in community patients showed no increase in pain intensity scores in patients who were able to taper their opioids by greater than 50% from the starting dose. The median opioid dose in the sample was 288 MED. The median duration of opioids was six years. Median pain intensity was moderate (5 out of 10 on a numeric pain rating). After four months, the median MED was reduced to 150 (IQR, 54-248) mg (P = .002). Of note, neither pain intensity (P = .29) nor pain interference (P = .44) increased with opioid reduction.¹⁶⁷³
- aa. Many patients on chronic opioid therapy are reluctant to taper. In addition, some physicians and authors question whether tapering is necessary if the patient is stable and adherent to their current dose. Yet it is well established that patients on high doses of opioids are at increased risk for a variety of side effects, serious morbidities, and death.¹⁶⁷⁴ Quality of life may be adversely affected, despite the fact that the patient perceives benefit in terms of pain relief. Indeed, as above, data show that in addition to reducing opioid-related risk, pain can improve when patients lower their opioids, which is evidence in and of itself that opioids do not work for chronic pain for those patients.
- bb. A newborn is born dependent on opioids as a result of being exposed to opioids *in utero*. According to DSM-5 criteria, the opioid dependent newborn is not “addicted,” because addiction requires the manifestations of certain pathological and maladaptive behaviors in conjunction with opioid use. The newborn is the passive recipient of opioids due to the mother’s exposure.
 - i. The rate of admission to neonatal intensive care units (“NICU”) for neonatal abstinence syndrome (“NAS”), a drug-withdrawal syndrome that occurs after in utero exposure to opioids, increased from 7 cases per 1000 admissions to 27 cases per 1000 admissions between 2004 and 2013.¹⁶⁷⁵
 - ii. Tolia reported that “the median length of stay increased from 13 days to 19 days (P<0.001 for both trends). The total percentage of NICU

¹⁶⁷² *Id.* at p. 318.

¹⁶⁷³ Darnall BD, Ziadni MS, Stieg RL, Mackey IG, Kao MC, Flood P. Patient-centered prescription opioid tapering in community outpatients with chronic pain. *JAMA Intern Med.* 2018. doi:10.1001/jamainternmed.2017.8709, at p. 708.

¹⁶⁷⁴ Gomes T, Mamdani MM, Dhalla Ia, Paterson JM, Juurlink DN. Opioid dose and drug-related mortality in patients with nonmalignant pain. *Arch Intern Med.* 2011;171(7):686-691. doi:10.1001/archinternmed.2011.117, at p. 686; see also Lembke *et al.*, Weighing The Risks,” fn. 5, above, at p. 982; Edlund *et al.*, Role of Opioid Prescription,” fn. 75, above, at p. 7; Chou *et al.*, “Effectiveness and Risks,” fn. 414, above, at p. ES-1.

¹⁶⁷⁵ Tolia VN, Patrick SW, Bennett MM, *et al.* Increasing incidence of the neonatal abstinence syndrome in U.S. neonatal ICUs. *Obstet Gynecol Surv.* 2015. doi:10.1097/OGX.0000000000000243, at p. 2118.

[neonatal intensive care unit] days nationwide that were attributed to the neonatal abstinence syndrome increased from 0.6% to 4.0% (P<0.001 for trend), with eight centers reporting that more than 20% of all NICU days were attributed to the care of these infants in 2013.”¹⁶⁷⁶

- iii. This approximate quadrupling of the rate of NAS is directly attributable to the epidemic of opioid use disorder that began with promotion of prescription opioids and continues to the present, accompanied by use of illicit opioid drugs.
- cc. Defendants’ promotional documents conveyed the message that prescription opioid dependence is not a significant concern, and that patients can be easily tapered off their prescriptions in a brief period of time. That message is contradicted by the scientific literature, my own clinical experience, and patients’ own accounts.¹⁶⁷⁷ This messaging improperly contributed to physicians’ false sense of security in the belief that prescription opioids can be prescribed without substantial risk. (See Appendix I). Further, misleading statements by Defendants on the efficacy of opioids in the treatment of chronic pain (see Appendix I) are inconsistent with the medical evidence that pain improves in many chronic pain patients who are tapered down and/or off of opioids.

11. Increased supply of prescription opioids contributed substantially to diversion of prescription opioids to individuals for whom they had not been prescribed (The Tsunami Effect).

- a. As stated in the 2013 CDC Report: “Almost all prescription drugs involved in abuse come from prescriptions originally. However, once they are prescribed and dispensed, prescription drugs are frequently diverted to people using them without prescriptions. There are instances where pharmacies are dispensing large quantities of opioids as part of an illegal distribution scheme as well as pharmacists who fail to meet their obligation to determine that a prescription was issued for a legitimate medical purpose.”¹⁶⁷⁸
- b. This quote highlights the large role that diversion of prescription opioids has played in the current epidemic. In addition to people getting addicted to and being harmed by opioids prescribed directly to them, millions have been harmed through diversion of prescription opioids to unauthorized sources, from teenagers experimenting to people already addicted to opioids gaining easier access through the illicit market.

¹⁶⁷⁶ *Id.* at p. 2118.

¹⁶⁷⁷ Rieder TN. In opioid withdrawal, with no help in sight. *Health Aff.* 2017;36(1):182-185. doi:10.1377/HLTHAFF.2016.0347

¹⁶⁷⁸ United States Department of Health and Human Services. Addressing Prescription Drug Abuse in the United States. :1-36, at p. 16. See https://www.cdc.gov/drugoverdose/pdf/hhs_prescription_drug_abuse_report_09.2013.pdf.

- c. An efficient distributor supply chain enabled opioid manufacturers to make prescription opioids available on a mass scale to large numbers of people in rural and remote settings, as well as urban and suburban settings, expanding both the licit and illicit drug market, and setting this opioid epidemic apart from prior epidemics and other drug epidemics. The sheer scale of access to opioids made possible through the distribution and supply chain, led individuals who otherwise would never have been exposed, to use and subsequently be killed or harmed by opioids.¹⁶⁷⁹
- d. As stated in a recent NASEM report, “the increase in the availability of drugs and both the long-term and increasing vulnerability of these population groups combined to create and fuel the rising trend in drug poisoning deaths. The country’s drug overdose crisis represents a ‘perfect storm’ of the flooding of the market with highly addictive yet deadly substances and underlying U.S. demand for and vulnerability to substances that temporarily numb both physical and mental pain.”¹⁶⁸⁰
- e. It is important to recognize that although many of the communities hit hardest by the opioid epidemic were already struggling with serious social and economic problems, the sudden availability of and easy access to opioids, initially in prescription pill form, contributed to the economic and social devastation of many towns across America.¹⁶⁸¹ Economic downturn and the efflux of manufacturing jobs in towns across America in the last thirty years, have contributed to so-called “deaths of despair” – early mortality in middle aged non-Hispanic whites due primarily to drug overdose.¹⁶⁸² In a March 2020 interview, co-author Angus Deaton further stated that “the economic and social distress has just been unwinding for a really, really long time. *And then the opioids threw fuel on that fire and turned it into a full raging epidemic.*”¹⁶⁸³ Nonetheless, economic disadvantage contributes only 10-20% of mortality risk attributable to opioids, whereas the larger share of risk is due to supply of opioids in a given geographic region.¹⁶⁸⁴
- f. ARCOS data on opioid prescribing show a 9% increase in opioid-related hospitalizations for each one morphine kilogram equivalent increase in opioid

¹⁶⁷⁹ See also §C.2.j, above, re likely extent of diversion of prescription opioids.

¹⁶⁸⁰ NASEM 2021, fn. 92, above, at p. 7-19.

¹⁶⁸¹ Ruhm CJ. Deaths of Despair or Drug Problems? NBER Working Paper No. 24188, NBER Program(s): Health Care, Health Economics, Public Economics, *National Bureau of Economic Research, Inc.* (2017).

¹⁶⁸² Case A, Deaton A. Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century. *Proc Natl Acad Sci.* 2015. doi:10.1073/pnas.1518393112, at p. 15081.

¹⁶⁸³ “Deaths of Despair – Case and Deaton Full”. <https://www.youtube.com/watch?v=jiPBEota8DI> (posted March 17, 2020).

¹⁶⁸⁴ Ruhm, *et al.*, “Deaths of Despair,” fn. 1681, above.

sales at the county level.¹⁶⁸⁵ These data demonstrate a clear and convincing relationship between opioid dispensing and opioid related harm.¹⁶⁸⁶

- g. Khan *et al.*, writing in *JAMA Internal Medicine* in 2019, show that an opioid prescription to one family member increases the risk of opioid overdose death to others in the same family, even though they do not have an opioid prescription. This study identifies 2,303 individuals who experienced opioid overdose and 9,212 matched control individuals, and shows that any prior opioid dispensing to family members was associated with overdose (odds ratio [OR], 2.89 [95% CI, 2.59-3.23]) in other family members. Risk of overdose increased in a dose-response fashion: Odds of overdose (>0-<50 morphine milligram equivalents per day: OR, 2.71 [95% CI, 2.42-3.03]; 50-<90 morphine milligram equivalents per day: OR, 7.80 [95% CI, 3.63-16.78]; ≥90 morphine milligram equivalents per day: OR, 15.08 [95% CI, 8.66-26.27]).¹⁶⁸⁷
- h. A 2021 study examining parents prescribed opioids for medical conditions found that their adolescent children are more likely to be prescribed opioids as well as misuse prescription opioids. The study found that “controlling for other factors, parental medical prescription opioid use was associated with adolescent prescription opioid medical use (adjusted odds ratio [aOR] 1.28; 95% CI, 1.06-1.53) and misuse (aOR, 1.53; 95% CI, 1.07-2.25), whereas parental misuse was not.”¹⁶⁸⁸ The authors found that “the association of parental medical prescription opioid use with adolescent prescription opioid misuse suggests that role modeling and availability of parents’ opioid medications in the household are significant familial risk factors for prescription opioid misuse among young people, although adolescents also misuse their own prescription opioid medications and prescriptions opioids from nonfamilial sources.”¹⁶⁸⁹
- i. A study of US 12th grade adolescents found that students attending schools with the highest rates of medical use of prescription opioids had a 57% increased odds of prescription opioid misuse, compared with schools that had no medical use of prescription opioids.¹⁶⁹⁰ “The robust association between school-level medical use of prescription opioids and POM [prescription opioid misuse] is consistent with evidence showing the largest sources of prescription

¹⁶⁸⁵ Ghertner R. U.S. County Prevalence of Retail Prescription Opioid Sales and Opioid-Related Hospitalizations from 2011 to 2014. *Drug and Alcohol Dependence* 194 (2019):330–335, at p. 330.

¹⁶⁸⁶ *Id.* at p. 333.

¹⁶⁸⁷ Khan NF, Bateman BT, *et al.* Association of Opioid Overdose with Opioid Prescription to Family Members. *JAMA Intern Med.* doi:10.1001/jamainternmed.2019.1064, at p. E3.

¹⁶⁸⁸ Griesler PC, *et al.* Assessment of prescription opioid medical use and misuse among parents and their adolescent offspring in the US. *JAMA Network Open.* 021;4(1):1-16, at p. 1.

¹⁶⁸⁹ *Id.* at p. 11.

¹⁶⁹⁰ McCabe SE, *et al.* Medical use and misuse of prescription opioids in US 12th grade youth: School-level correlates. *Pediatrics.* 2020;146(4):1-13, at p. 1.

opioids among adolescents are peers and leftover medication.”¹⁶⁹¹ The authors state that this association has weakened in recent years, which may be due to the impact of efforts to reduce prescription opioid misuse, or because adolescents “are turning to more readily available substances (e.g., marijuana, heroin) as prescription opioids become less available.”¹⁶⁹²

- j. The recent NASEM report on guidelines for opioid use for acute pain (NASEM 2020), referenced above, further states that “Opioids pose risks not only to the patients for whom they are prescribed, but also to family members and to the community. Unused opioid pills from opioid prescriptions can be diverted to family members and friends (Bicket *et al.*, 2019; Hill *et al.*, 2017; Howard *et al.*, 2019; Thiels *et al.*, 2017). These unused pills, which often are not disposed of properly, may be used by the patient for indications other than those for which they were prescribed (e.g., as a sleep aid), or they may be used by someone other than the patient (Bicket *et al.*, 2017; Jones *et al.*, 2014). Individuals with opioid use disorder commonly report that they started by misusing prescription opioids (Ali *et al.*, 2019; Becker *et al.*, 2008; Cicero *et al.*, 2014; NASEM, 2019). Furthermore, there is an association between the size of a patient’s opioid prescription and the likelihood of an opioid overdose among the patient’s family members (Khan *et al.*, 2019). This association is present in children and adolescents as well as in adults (Khan *et al.*, 2019). Among individuals who misuse prescription opioids, the most common source of opioids was pills from family members and friends. Among individuals who use heroin, the majority (66%) previously misused prescription opioids (Cicero *et al.*, 2014). *Thus, opioid overprescribing, that is, prescribing more opioids than are necessary to control a patient’s acute pain, is a factor contributing to the public health epidemic of opioid overdoses.*”¹⁶⁹³
- k. Opioid overprescribing after surgery is a significant contributor to the Tsunami Effect. A recent study reported that 83% of US patients who reported no pain after operation were discharged on opioids compared with 8.7% of non-US patients (p<0.001).¹⁶⁹⁴ After discharge, the number of opioid prescription refills was substantially higher among US patients compared with non-US patients (7.1% vs 0.1%; p<0.001).¹⁶⁹⁵ US patients were also prescribed more pills in higher doses than their non-US counterparts. The mean adjusted OME [oral morphine equivalent] and number of pills for US patients increased from 156.1 OME and 20.6 pills in US patients without pain, to 213.4 OME and 27.1 pills in US patients with severe pain, compared to non-US prescribing of 9.8

¹⁶⁹¹ *Id.* at p. 8.

¹⁶⁹² *Id.* at p. 9.

¹⁶⁹³ NASEM 2020, fn. 1655, above, at pp. 15-16 (emphasis added).

¹⁶⁹⁴ El Moheb M, *et al.* Pain or No Pain, We Will Give You Opioids: Relationship between number of opioid pills prescribed and severity of pain after operation in U.S. vs non-U.S. patients. *J Am Coll Surg.* 2020;231(6):639-648, at p. 642-644.

¹⁶⁹⁵ *Id.* at p. 642.

OME and 1.4 pills in non-US patients without pain and 26.8 OME and 4.5 pills in non-US patients with severe pain.¹⁶⁹⁶ The authors state that “The large quantity of unused pills increases the risk of opioid misuse and diversion to the community at large.”¹⁶⁹⁷ The frequent and completely unnecessary prescription of powerful and addictive drugs to patients who are not experiencing any degree of pain is emblematic of the extent to which the Defendants’ false messages of prescription opioid safety, and their ubiquitous distribution, have permeated the medical profession and continue to exert their harmful influence.

1. Finally, an objective observer would have appreciated that the number of opioid pills being shipped to pharmacies all over the United States was far in excess of medical need. Annual Production Quotas (APQs) that were approved by the DEA, despite FDA recommendations for lower amounts, were based on unsupported Industry claims of market demand, without consideration of the obvious concern that the requested APQs included substantial diversion that contributed to the prescription opioid epidemic. While the DEA bears some responsibility for routinely accepting sales figures and unsupported claims of increased demands as a proxy for legitimate needs,¹⁶⁹⁸ the Industry itself bears primary responsibility for submitting requests for APQs that “were clearly excessive from 2010-2016.”¹⁶⁹⁹

12. The increased supply of prescription opioids through licit and illicit sources resulted in a prescription opioid epidemic in the United States. “Epidemic,” defined as an outbreak of disease that spreads quickly and affects many individuals at the same time, is the appropriate term to describe the increase in opioid related morbidity and mortality beginning in the 1990’s and continuing to the present day.

- a. The Stanford-*Lancet* Commission described the evolution and continuing threat resulting from the overprescribing and oversupply of prescription opioids, stating that “[t]he opioid crisis has shown that in the absence of adequate supply control over addictive drugs, damage to human health and wellbeing is unavoidable.”¹⁷⁰⁰ Further, the harms of the opioid epidemic are urgent and ongoing: “Large numbers of US and Canadian people are still becoming addicted to prescription opioids each year, and most of those who die from heroin and fentanyl overdoses are previous or current users of prescription opioids.”¹⁷⁰¹ The Commission’s opioid crisis model estimates

¹⁶⁹⁶ *Id.* at p. 643.

¹⁶⁹⁷ *Id.* at p. 646.

¹⁶⁹⁸ State of West Virginia Office of the Attorney General, “DEA’s Failure to Combat Diversion Cost Lives: results from the West Virginia Attorney General’s Investigation into the DEA’s catastrophic failure to manage the National Drug Quota System from 2010-2016, (June 4, 2020), at p. 29

¹⁶⁹⁹ *Id.* at p. ES-4.

¹⁷⁰⁰ Stanford-*Lancet* Commission, fn 17, above, at p. 5.

¹⁷⁰¹ *Id.*

that, in the absence of any intervention, an additional 1,220,000 fatal opioid overdoses will occur in the US between 2020 and 2029.¹⁷⁰²

- b. The societal effects of this opioid epidemic are worse than the societal effects of other drug epidemics, because of the accelerated devastation to individuals and communities, including (i) high rates of addiction and death in young people in the prime of their lives; (ii) high rates of pregnant women being exposed to opioids and giving birth to babies dependent on opioids, who in turn suffer long-term cognitive consequences;¹⁷⁰³ (iii) the tragic disruption to families and communities due to loss of parental caregivers,¹⁷⁰⁴ requiring substantial resources for foster care; and (iv) exodus from the work force as a result of opioid dependence and addiction.¹⁷⁰⁵

- i. Long-term effects of Prenatal Opioid Exposure (“POE”)

- A. In a recent *JAMA* meta-analysis, the authors reported statistically significant cognitive and motor deficits among children exposed to prenatal opioids compared to unexposed children, from birth through age 6; deficits found among children from age 7-18 were no longer statistically significant.¹⁷⁰⁶ The authors stated, “The cause and association of this with POE or other factors (*e.g.*, withdrawal treatment) are uncertain but suggest that POE necessitates long-term support and intervention.”¹⁷⁰⁷ It should be noted that, to the extent that “withdrawal treatment” may be a cause of the observed deficits, such treatment itself would not have been required if not for the POE that precipitated the withdrawal and accompanying need for treatment. Further, “children with POE are 3 times more likely to have severe intellectual disability according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition criteria Poor neurodevelopmental outcomes in children with POE, even from an early age, is not novel information. However, our data appear to indicate that neurodevelopment did not improve after preschool and worsened by school age.”¹⁷⁰⁸

¹⁷⁰² Stanford-Lancet Commission, fn 17, above, at p. 12.

¹⁷⁰³ Yeoh SJ, *et al.* Cognitive and motor outcomes of children with prenatal opioid exposure: a systemic review and meta-analysis. *JAMA Network Open*. 2019; 2(7): 1-14, at pp. 1-2.

¹⁷⁰⁴ Radel L, Baldwin M, *et al.* Substance use, the opioid epidemic, and the child welfare system: key findings from a mixed methods study. *ASPE Research Brief*. (March 7, 2018)

¹⁷⁰⁵ Franklin GM, *et al.* Early opioid prescription and subsequent disability among workers with back injuries. *Spine*. 2008; 33(2): 199-204; *see also* Anora M. Gaudiano, *How the opioid epidemic is exacerbating a US labor-market shortage*. MarketWatch, June 29, 2018. <https://www.marketwatch.com/story/how-the-opioid-epidemic-is-exacerbating-a-us-labor-market-shortage-2018-06-28>.

¹⁷⁰⁶ Yeoh, “Cognitive and Motor Outcomes”, fn. 1703, above.

¹⁷⁰⁷ *Id.* at p. 2.

¹⁷⁰⁸ *Id.* at pp. 8-9.

- B. Similar results were reported in a study of the academic testing of Australian children who had been diagnosed with NAS at birth. Test scores of NAS children were compared to those of matched controls and the general population, at Grades 3, 5, 7, and 9, which correspond to ages 8-9, 10-11, 12-13, and 14-15, respectively. The authors reported, “Our results show that a diagnosis of NAS is associated with poorer performance in standardized and compulsory curriculum-based tests from as early as 8 or 9 years of age in grade 3 of school when compared with other NSW [New South Wales] children, including those who were matched for gender, gestation, and socioeconomic status. Indeed, by the first year of high school, children with NAS performed even more poorly than other children in grade 5 who were, on average, 2 years younger. By grade 7, 44% of children with NAS had failed to meet NMS [National Minimum Standards] in ≥ 1 domain of testing.”¹⁷⁰⁹
- C. While noting that the cause for these effects is “uncertain,” the authors cited known biological mechanisms that could reasonably explain the deficits: “NAS is caused by transplacental exposure to drugs of addiction or dependency that interfere with brain function and development. Opioids impair adult brain function and cognitive skills even after only a few days of use, and their effects on the developing brain are subtle but long-lasting and include alterations to neuronal apoptosis, dendritic morphogenesis, and neurotransmitter homeostasis.”¹⁷¹⁰ Further, the risk of failure to meet NMS (OR=2.5) was greater for NAS than for any other risk factor investigated.¹⁷¹¹
- D. The consistency of results from the Yeoh and Oei studies provides support for the conclusion that NAS contributes substantially to persistent developmental deficits. “This finding is of great concern because school failure increases the risk of myriad poor adult outcomes, including depression in women, criminal activity, and drug use. We showed that children with NAS performed more poorly in all 5 test domains, including reading or literacy skills, 1 of the most important predictors of school success. Children who cannot

¹⁷⁰⁹ Oei JL, *et al.* Neonatal Abstinence Syndrome and High School Performance. *Pediatrics*. 2017;139(2):e20162651, at p. 7.

¹⁷¹⁰ *Id.*

¹⁷¹¹ *Id.*

read at expected levels by grade 3 are less likely to enroll in college or graduate high school. In the United Kingdom, two-thirds of prisoners have a reading age <11 years. Furthermore, test results in children with NAS worsened as they entered high school.”¹⁷¹²

E. A recent study found developmental delays among infants exposed to opioids in utero, even where the newborns displayed no overt symptoms of NAS. The authors reported, “Compared to infants with no detected exposures the diagnosis of developmental delay was highest among infants with NAS (7.6% versus 28.3%). However, the diagnosis was still twice as likely among opioid exposed infants without NAS (7.6% versus 15.6%).”¹⁷¹³

- ii. Loss of Parental Caregivers and Impacts on Foster Care: A 2018 study of the relationship between drug use and foster care reported, “Higher rates of overdose deaths and drug hospitalizations correspond with higher child welfare caseload rates. We estimate that in the average county nationwide, a 10 percent increase in the overdose death rate corresponded to a 4.4 percent increase in the foster care entry rate. Similarly, a 10 percent increase in the average county’s drug-related hospitalization rate corresponded to a 2.9 percent increase in its foster care entry rate.”¹⁷¹⁴ While the increased rates of overdose deaths are not exclusively linked to opioids, data cited previously support the significantly greater share of drug mortality attributable to opioids than to other drugs.¹⁷¹⁵
- iii. Exodus from the workforce: It is well-known that widespread distribution and use of opioids has had a significant adverse effect on the availability of workers, both due to increased mortality and the myriad problems associated with opioid use. According to a recent analysis, “The opioid epidemic is preventing a huge portion of the population that is sidelined from joining the labor force because labor intensive jobs are also the ones that require workers who can pass drug

¹⁷¹² *Id.*

¹⁷¹³ Hall ES *et al.* Developmental disorders and medical complications among infants with subclinical intrauterine opioid exposures. *Population Health Management*. 2019;22:19-24, at p. 21.

¹⁷¹⁴ Radel, “Child Welfare System”, fn. 1704, above, at pp. 2-3.

¹⁷¹⁵ See, e.g., Centers for Disease Control and Prevention, *Opioid Overdose*, <https://www.cdc.gov/drugoverdose/index.html>: “Drug overdose deaths continue to increase in the United States. From 1999 to 2017, more than 702,000 people have died from a drug overdose. In 2017, more than 70,000 people died from drug overdoses, making it a leading cause of injury-related death in the United States. Of those deaths, almost 68% involved a prescription or illicit opioid.” (emphasis added).

tests.”¹⁷¹⁶ The opioid epidemic is responsible for this detrimental impact. Franklin (2008) found that “receipt of opioids for more than 7 days (odds ratio 2.2; 95% confidence interval, 1.5-3.1) and receipt of more than 1 opioid prescription were associated significantly with work disability at 1 year.” Another study of long-term opioid use and opioid use disorder among construction workers found that “workers prescribed long-term opioids in any calendar quarter had a nearly 10-fold odds of developing an OUD.”¹⁷¹⁷ An additional study of labor force loss due to opioids estimates 919,400 individuals out of work force due to opioids in 2015.¹⁷¹⁸

c. Overdose (“OD”) deaths

- i. A study by Dunn *et al.* found an increased risk of opioid-related overdose death in a step-wise dose response relationship: “Compared with patients receiving 1 to 20 mg/d of opioids (0.2% annual overdose rate), patients receiving 50 to 99 mg/d had a 3.7-fold increase in overdose risk (95% CI, 1.5 to 9.5) and a 0.7% annual overdose rate. Patients receiving 100 mg/d or more had an 8.9-fold increase in overdose risk (CI, 4.0 to 19.7) and a 1.8% annual overdose rate. ... Patients receiving higher doses of prescribed opioids are at increased risk for overdose, which underscores the need for close supervision of these patients.”¹⁷¹⁹ The HRs from the Dunn study are represented in the graph at paragraph §C.12.c., below.
- ii. Dunn reported that 4 of the 51 overdose cases (7.8%) “had notes indicating overdoses associated with applying extra fentanyl patches or sucking on a patch.”¹⁷²⁰ The percentage of overdose cases attributed to fentanyl is much higher than the relatively minor percentage of patients in the study population who used the fentanyl patch (0.6%).¹⁷²¹ This is consistent with fentanyl’s known lethality (50-100 times as potent as heroin), which increases the risk of overdose and death.

¹⁷¹⁶ Anora M. Gaudiano, *How the Opioid Epidemic Is Exacerbating a US Labor-Market Shortage*, MarketWatch (June 29, 2018), <https://www.marketwatch.com/story/how-the-opioid-epidemic-is-exacerbating-a-us-labor-market-shortage-2018-06-28>.

¹⁷¹⁷ Dale AM, *et al.* Predictors of long-term opioid use and opioid use disorder among construction works: Analysis of claims data. *Am J Ind Med.* 2021;64(1):48-57, at p. 48

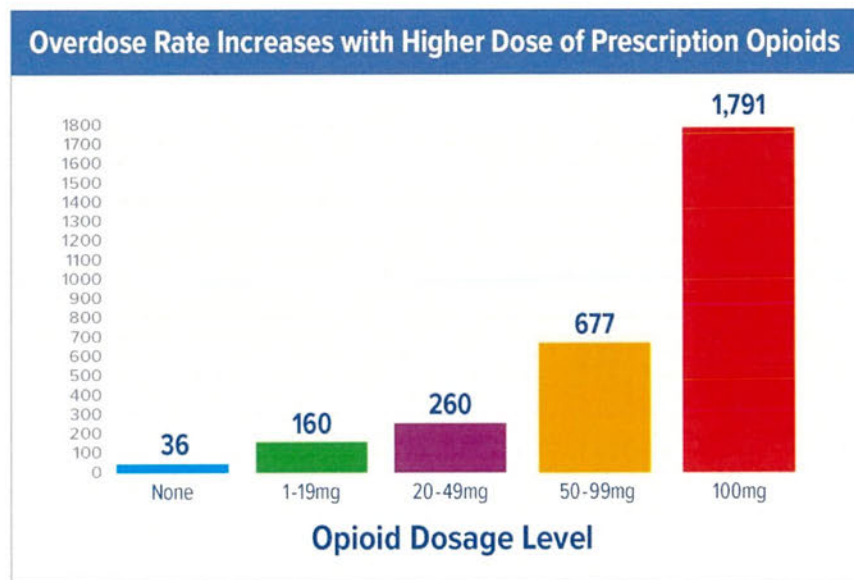
¹⁷¹⁸ Ben Gitis, Isabel Soto, *The Labor Force and Output Consequences of the Opioid Crisis*, American Action Forum (Mar. 27, 2018), <https://www.americanactionforum.org/research/labor-force-output-consequences-opioid-crisis/>.

¹⁷¹⁹ Dunn KM, Saunders KW, Rutter CM, *et al.* Opioid prescriptions for chronic pain and overdose: A cohort study. *Ann Intern Med.* 2010;152(2):85-92, at p. 85.

¹⁷²⁰ *Id.* at p. 88.

¹⁷²¹ *Id.* at Table 1, p. 88.

- iii. In the Dunn study, the authors noted that the risk analysis was based on a comparison of overdose events among higher dose patients to those who received lower doses, rather than the patients who received none.¹⁷²² The authors also provided data on the rate of ODs at all levels of exposure, including those with no exposure, and these data further demonstrate the magnitude of increased risk. For the population with no prescribed opioids, the OD rate was 36 per 100,000 person years (PYR), while increasing to 677 per 100,000 PYR at doses of 50-99 mg, and 1791 per 100,000 PYR at doses of 100 mg or greater, representing rate increases of 18.8 and 49.8, respectively, compared to no prescription opioid use.¹⁷²³ These data are represented in the graph below:



SOURCE: Dunn 2010

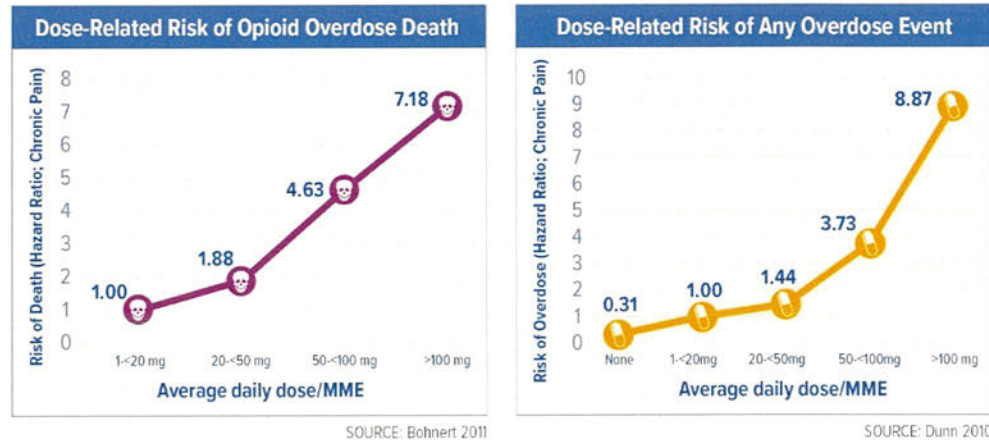
- iv. Dunn also noted that their study “provides the first estimates that directly link receipt of medically prescribed opioids to overdose risk, and suggests that overdose risk is elevated in patients receiving medically prescribed opioids, particularly in patients receiving higher doses.”¹⁷²⁴ These are important data, since they directly refute the Industry’s position that only those who misuse the drugs are at risk of OUD and mortality.

¹⁷²² *Id.* at p. 90

¹⁷²³ *Id.* at Table 3, p. 89.

¹⁷²⁴ *Id.* at p. 90.

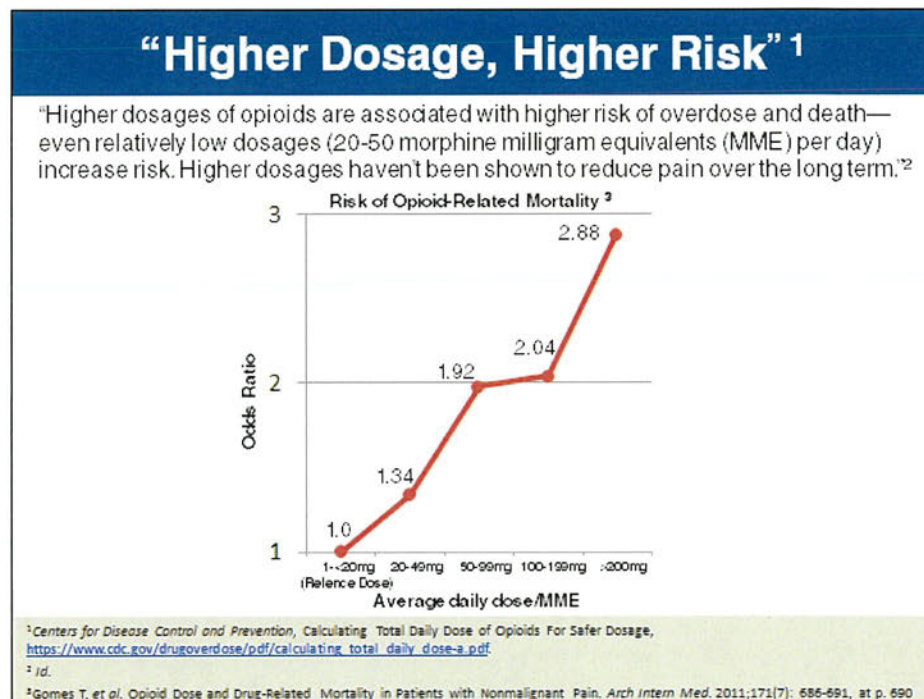
CDC: “HIGHER DOSAGE, HIGHER RISKS”



- v. As shown in the graph above, studies by Dunn *et al.* and by Bohnert *et al.* both found an increased risk of opioid-related overdose death at each level of increased dose, and particularly at doses greater than 100 MME. In the Dunn study, compared to the reference dose of 1-<20 mg, the adjusted hazard Ratio (HR) for 20-<50 mg was 1.44; for 50-100 mg, the HR was 3.73; and for > 100 mg, the HR was 8.87. In the Bohnert study, compared to the same reference dose of 1 to < 20 MME, the HR for 20 to < 50 mg was 1.88; for 50 to < 100 mg, the hazard ratio was 4.63; and at > 100 mg, the hazard ratio was 7.18. All results were statistically significant. A similar pattern held for each of three diagnostic groups in the Bohnert study (substance use disorders, chronic pain, and cancer): “The adjusted hazard ratios (HRs) associated with a maximum prescribed dose of 100 mg/d or more, compared with the dose category 1 mg/d to less than 20 mg/d, were as follows: among those with substance use disorders, adjusted HR = 4.54 (95% confidence interval [CI], 2.46-8.37; absolute risk difference approximation [ARDA] = 0.14%); among those with chronic pain, adjusted HR = 7.18 (95% CI, 4.85-10.65; ARDA = 0.25%); among those with acute pain, adjusted HR = 6.64 (95% CI, 3.31-13.31; ARDA = 0.23%); and among those with cancer, adjusted HR = 11.99 (95% CI, 4.42-32.56; ARDA = 0.45%).”¹⁷²⁵ Opioid therapy is generally accepted as appropriate for cancer patients, especially in late stages or severe pain. Nevertheless, with the advent of improved cancer therapies, more patients are living longer with disease or remission, and opioid therapy should be implemented with caution, to minimize risk of addiction.

¹⁷²⁵ Bohnert, *et al.*, “Association Between Prescribing Patterns,” fn. 1624, above, at p. 1315; Olsen, *et al.*, “Pain relief that matters,” fn. 1336, above.

- vi. According to the CDC, the studies referenced above support the conclusion that approximately 60% of fatal prescription opioid overdoses occurred among patients taking medically prescribed opioids from a single prescriber.¹⁷²⁶
- vii. A population based nested case control study of 607,156 people prescribed opioids found that an average daily dose of 200 mg or more of morphine or equivalent was associated with a nearly 3-fold, statistically significant increased risk of opioid-related mortality relative to low daily doses (< 20 mg of morphine or equivalent), Odds Ratio (OR) 2.88, 95% CI 1.79-4.63.¹⁷²⁷ This is illustrated in the graph below:



- viii. A study of U.S. adolescents and young adults found that “approximately 1 in 10,000 adolescents and young adults overdosed

¹⁷²⁶ Paulozzi L, et al. CDC Grand Rounds: Prescription drug overdoses – a U.S. epidemic. *MMWR Morb Mortal Wkly Rep.* 2012;61(1):1-37, at p. 10. See also: Manchikanti, “ASIPP Guidelines”, fn. 415, above, at p. S10.

¹⁷²⁷ Gomes et al, “Opioid Dose,” fn. 1674, above, at p. 686. It is noteworthy that Gomes studied “Non-Malignant Pain,” without regard to duration of exposure, requiring only “at least one” opioid prescription in the 120 days prior to death. (p. 687) This may explain the lower relative risk in the Gomes study compared to those in Bohnert (study of pain patients specified those with “chronic pain” conditions) and Dunn (inclusion criteria required 3 or more opioid prescriptions within 90 days prior to the overdose). As Edlund demonstrated, duration of exposure is a key factor in determining the magnitude of increased risk of opioid-related harm.

while they had an active opioid prescription.”¹⁷²⁸ Further, in adjusted analyses “each increase in daily opioid dosage category was associated with an 18% higher odds of overdose.”¹⁷²⁹

- ix. A recent retrospective cohort study of over 2 million individuals newly dispensed an opioid for pain between July 2013 and March 2016 found that 525 of 1121 overdoses (46.8%) occurred while patients were actively being treated with prescription opioids,¹⁷³⁰ which further supports that patients using opioids for medical reasons are at risk of overdose. The study further found that 289 of 1121 (25.5%) of the overdoses occurred within the first 28 days following initiation of the prescription and that the odds of long-term use (> 1 year) were 8-fold higher with > 30 days initial prescription compared to 2 days or less initial prescription length, and even prescriptions of 3-4 days conferred a 19% increased risk of OD compared to 2 days or less.¹⁷³¹ While the study cannot rule out that patients may have been using non-prescribed opioids along with the prescribed opioids, the fact that nearly half were in active treatment, and that the risk increased with the prescribed dose, strongly implicate the prescription opioids as at least contributing factors to the overdoses.
- x. A 2019 cohort study from the United Kingdom examined 98,140 new long-term (three or more opioid prescriptions within 90 days) opioid users for 3.4 years. The authors found that “[l]ong-term opioid use is associated with serious adverse events such as major trauma, addiction and overdose. The risk increases with higher opioid doses.”¹⁷³²
- xi. The evidence of increased dose as the cause of higher mortality is supported by evidence of the converse, that is, lower mortality following decreased dose. Recent experience in Oregon demonstrated a significant decrease in overdose deaths after policies were implemented to prioritize non-opioid pain management and to lower the doses when opioid therapy was prescribed.¹⁷³³

¹⁷²⁸ Chua K-P, Brummett CM, Conti RM, Bohnert A. Association of opioid prescribing patterns with prescription opioid overdose in adolescents and young adults. *JAMA Pediatr.* 2020;174(2):141-148, at p. 146.

¹⁷²⁹ *Id.*

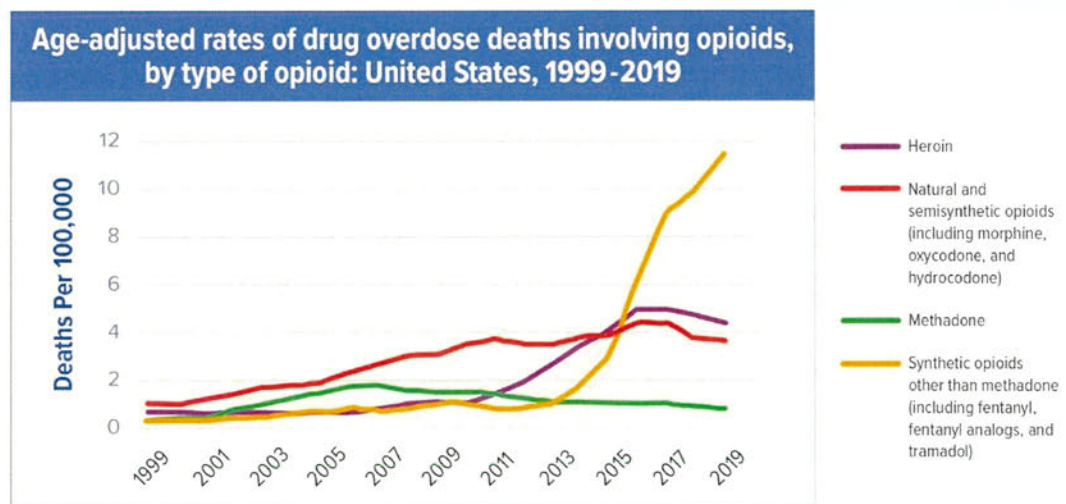
¹⁷³⁰ Gomes T, *et al.* Initial opioid prescription patterns and the risk of ongoing use and adverse outcomes. *Pharmacoepidemiol Drug Saf.* 2020:1-11, at p. 6.

¹⁷³¹ *Id.* at pp. 6, 8.

¹⁷³² Bedson J, Chen Y, Ashworth J, Hayward RA, Dunn KM, Jordan KP. Risk of adverse events in patients prescribed long-term opioids: A cohort study in the UK Clinical Practice Research Datalink. *Eur J Pain.* 2019; 23:908-922, at p. 908.

¹⁷³³ Hedberg K, *et al.* Integrating public health and health care strategies to address the opioid epidemic: the Oregon Health Authority’s opioid initiative. *Journal of Public Health Management & Practice.* 2019;25(2):214-220, at pp. 214-215.

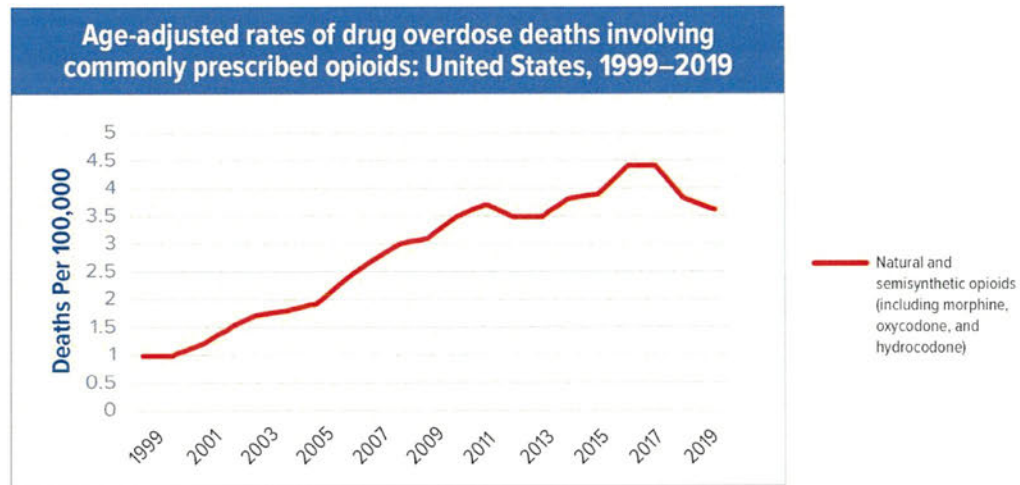
- xii. We are now in the second and third waves of this epidemic, with a spike in deaths from illicit opioids, particularly heroin (second wave) and illicit fentanyl (third wave). The prescription opioid epidemic led to transition to heroin/fentanyl, and the cumulative death toll remains higher for prescription opioids, despite recent spikes in fentanyl-related mortality. Further, some researchers have noted a recent increase in stimulant involvement in opioid-related mortality, which varies by region, and is sometimes described as a “4th wave” of the opioid epidemic.¹⁷³⁴
- xiii. Based on CDC data, between 1999 and 2018, 245,218 people died from opioid pain relievers (excluding non-methadone synthetics, predominantly fentanyl). In the same time period, 115,568 died from heroin, and 124,486 people died from non-methadone synthetics (predominantly fentanyl), for a total of 240,054 deaths due to heroin and illicit fentanyl. Although these numbers are staggering, the cumulative death toll from opioid pain relievers through 2018 (245,218) was more than that of heroin and illicit fentanyl combined (240,054).¹⁷³⁵ The graphs below show the changes in opioid death rates over time.¹⁷³⁶



¹⁷³⁴ Friedman J, Shover CL. Charting the fourth wave: Geographic, temporal, race/ethnicity and demographic trends in polysubstance fentanyl overdose deaths in the United States, 2010-2021. *Addiction*. 2023;118:2477-2485. See also: O'Donnell J, et al. Trends in and characteristics of drug overdose deaths involving illicitly manufactured fentanyls – United States, 2019-2020. *MMWR*. 2021;70(50):1740-1746

¹⁷³⁵ Centers for Disease Control and Prevention, *Data Brief 356. Drug Overdose Deaths in the United States, 1999–2018*, https://www.cdc.gov/nchs/data/databriefs/db356_tables-508.pdf, at Data Table for Figure 3,

¹⁷³⁶ Graphs generated from data provided by *Id.*

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- xiv. Prescription opioid related deaths, excluding fentanyl and methadone, continued to rise through 2017, with 2018 registering the first substantial annual decline in prescription opioid related deaths since 1999 (14,495 deaths in 2017; 12,550 in 2018).¹⁷³⁷ A 2019 report released by the CDC shows that drug overdose deaths in women aged 30–64 years due to prescription opioids have been steadily rising between 1999 and 2017. “The crude rate for deaths involving prescription opioids increased from 1999 to 2017 for every age group, with the largest increases (>1,000%) among women aged 55–64 years.”¹⁷³⁸
- xv. In 2019, 36,659 drug overdose deaths involved non-methadone synthetic opioids (primarily illicitly manufactured fentanyl), 14,019 deaths involved heroin and 14,626 deaths involved opioid pain relievers.¹⁷³⁹
- xvi. Provisional data for the period May 2019–May 2020 show “the highest number of overdose deaths ever recorded in a 12-month period” with over 81,000 drug overdose deaths.¹⁷⁴⁰ Synthetic opioids (illicitly manufactured fentanyl) “appear to be the primary driver of the increases in overdose deaths” with 10 western states reporting an over 98% increase in fentanyl-involved overdose deaths.¹⁷⁴¹ According to

¹⁷³⁷ *Id.*¹⁷³⁸ VanHouten JP, Rudd RA, Ballesteros MF, Mack KA. Drug Overdose Deaths Among Women Aged 30–64 Years — United States, 1999–2017. *MMWR Morb Mortal Wkly Rep.* 2019;68(1):1–5, at p. 2.¹⁷³⁹ Hedegaard H. *et al.* Drug overdose deaths in the United States, 1999–2019. NCHS Data Brief No. 394, at Data Table for Figure 3. <https://www.cdc.gov/nchs/products/databriefs/db394.htm>¹⁷⁴⁰ Centers for Disease Control and Prevention, Overdose deaths accelerating during Covid-19, (December 17, 2020), <https://www.cdc.gov/media/releases/2020/p1218-overdose-deaths-covid-19.html>, at p. 1.¹⁷⁴¹ *Id.*

the CDC, “While overdose deaths were already increasing in the months preceding the 2019 novel coronavirus disease (COVID-19) pandemic, the latest numbers suggest an acceleration of overdose deaths during the pandemic.”¹⁷⁴²

- xvii. Younger cohorts were particularly vulnerable to opioid-related mortality during the COVID-19 pandemic. In the years 2020 and 2021, more than 20% of deaths among those aged 20-39 years old and 10% of those aged 15-19 resulted from prescribed and/or unregulated opioids.¹⁷⁴³ “The absolute number of unintentional deaths due to opioid toxicity and the associated YLL [years of life lost] among those under 40 years far exceeded those attributable to COVID-19 in both 2020 and 2021.”¹⁷⁴⁴
- xviii. Although the National Institute on Drug Abuse recently stated that “commonly prescribed opioids are no longer driving the overdose crisis”¹⁷⁴⁵ prescription opioids nevertheless remain a substantial primary and contributing factor in US overdose mortality, as reflected in the chart below, based on government data:¹⁷⁴⁶

Overdose deaths	2020	2021
Prescription Opioids (all)	16,416	16,706
Prescription Opioids and synthetic opioids other than Methadone	8,626	9,644
Prescription Opioids without synthetic opioids other than Methadone	7,790	7,062
Synthetic Opioids (primarily fentanyl)	56,516	70,601
Heroin (all)	13,165	9,173

¹⁷⁴² *Id.*

¹⁷⁴³ Gomes T, *et al.* Trends in opioid toxicity-related deaths in the US before and after the start of the COVID-19 pandemic, 2011-2021. *JAMA Network Open.* 2023;6(7):1-7, at p. 3.

¹⁷⁴⁴ *Id.*, at p. 5.

¹⁷⁴⁵ National Institute on Drug Abuse. *Drug Overdose Death Rates* (June 30, 2023), <https://nida.nih.gov/research-topics/trends-statistics/overdose-death-rates>

¹⁷⁴⁶ National Institute on Drug Abuse. *National Drug Overdose (OD) Deaths, 1999-2021* (excel file). See also: Centers for Disease Control and Prevention. *Data Brief 491. Drug Overdose Deaths in the United States, 2002-2022*, <https://www.cdc.gov/nchs/data/databriefs/db491.pdf>, at p. 4, Figure 4 and footnote 2.

- xix. In short, as shown in the graphs above, while there has been an obvious recent spike in deaths related to heroin and illicit fentanyl, the number of deaths caused by non-fentanyl prescription opioids has continued to be unacceptably high, and approximately four times greater than in 1999.
- d. Nonfatal overdose
 - i. While fatal cases justifiably capture our attention, it must also be recognized that the cost of a nonfatal overdose is far greater in terms of medical and community resources, both in terms of medical costs to treat the overdose episode itself, and to provide long-term care for an OUD that may have given rise to the overdose event.
 - ii. According to the CDC, among approximately 45 million emergency department visits reported by the 16 Enhanced State Opioid Overdose Surveillance (ESOOS) states from July 2016 through September 2017, “a total of 119,198 (26.7 per 10,000 visits) were suspected opioid overdoses.”¹⁷⁴⁷
 - iii. Unlike the available fatal overdose data, which are categorized according to non-fentanyl prescription opioids, heroin, etc., the CDC/ESOOS on emergency department visits are not broken out into categories. Although the cumulative total of prescription opioid mortality since 1999 exceeds mortality for fentanyl plus heroin, the mortality rate for the latter category has recently begun to exceed the former; it is likely that the nonfatal overdose hospital admissions have occurred in a similar ratio of prescription opioids to illicit heroin and fentanyl.
 - iv. A 2023 study of opioid overdose mortality risk following a non-fatal overdose found that in the year following the index overdose, the overdose incidence rate (fatal or non-fatal) was 23.3 per 100 person-years and that repeat opioid overdose incidence was highest in the first 30 days following the index overdose.¹⁷⁴⁸ Another 2023 study of opioid overdose found that 12.1% of opioid overdose survivors had a repeat overdose within 1 year.¹⁷⁴⁹ Despite evidence that medications for opioid use disorder (eg, buprenorphine, methadone) significantly

¹⁷⁴⁷ Vivolo-Kantor AM, Seth P, Gladden RM, *et al.* Vital Signs: Trends in Emergency Department Visits for Suspected Opioid Overdoses — United States, July 2016–September 2017. *MMWR Morb Mortal Wkly Rep.* 2018;67:279–285, at p. 281.

¹⁷⁴⁸ Hood JE, *et al.* Overdose and mortality risk following a non-fatal opioid overdose treated by Emergency Medical Services in King County, Washington. *Drug Alcohol Depend.* 2023;253:1-8, at p. 1.

¹⁷⁴⁹ Tipping AD, *et al.* Medications for opioid use disorder are associated with reduced risk of repeat overdose in Medicaid: A cohort study. *Journal of Substance Use and Addiction Treatment.* 2023. [journal pre-proof]

reduce the risk of repeat opioid overdose,¹⁷⁵⁰ only 10.7% of patients received MOUD in the year after the index overdose.¹⁷⁵¹

- v. Tens of thousands of Americans experience non-fatal overdose, both in medical settings, like the emergency department, and in the field, creating a significant burden on the health care system and on first responders, not to mention the victims of near overdose themselves. In the paper by Dunn *et al.*, previously discussed, the authors found “[m]ore than 7 nonfatal overdose events occurred for each fatal overdose” in the study cohort.¹⁷⁵² “The overall overdose rate in the sample was 148 per 100,000 person-years, indicating that fatal overdose represents only the tip of the iceberg (88% of identified overdose events were nonfatal). Most of the nonfatal overdoses were clinically serious.”¹⁷⁵³ These data mean that on a nationwide basis, the over 14,000 fatal prescription opioid overdoses in 2017¹⁷⁵⁴ would translate to over 100,000 nonfatal overdoses during that same year.
- e. Suicide
 - i. The 2019 cohort study from the United Kingdom which examined 98,140 new long-term (three or more opioid prescriptions within 90 days) opioid users for 3.4 years, and found that long-term use was associated with serious adverse events, also found that the risk of suicide by intentional overdose increases with higher opioid doses.”¹⁷⁵⁵ The authors also report that intentional opioid overdose was nearly 4x more likely in patients prescribed long-term opioids at the highest doses (>50mg).¹⁷⁵⁶
 - ii. Writing in the journal *Pain*, Ilgen *et al.* found that the higher the dose of opioids, the greater the suicide risk, an association which was not present in patients with chronic pain on acetaminophen, a non-opioid pain pill. The authors write, “Increased dose of opioids was found to be a marker of increased suicide risk, even when relevant demographic

¹⁷⁵⁰ Heimer R, *et al.* Receipt of opioid use disorder treatment prior to fatal overdoses and comparison to no treatment in Connecticut, 2016-2017. *Drug and Alcohol Dependence*. 2023;254:1-7, at p. 1; *see also* Tipping, “Medications for opioid use disorder”, fn. 1749, above.

¹⁷⁵¹ Tipping, “Medications for opioid use disorder”, fn. 1749, above.

¹⁷⁵² Dunn, *et al.*, “Opioid Prescriptions,” fn. 1719, above, at p. 89. For overdoses involving synthetic opioids, in 2020, the rate is now ~2 fatal ODs for every non-fatal OD, demonstrating the increasing risk of OD mortality from synthetic opioid exposure. *See*: Casillas SM, Pickens CM, Tanz LJ, Vivolo-Kantor AM. Estimating the ratio of fatal and non-fatal overdoses involving all drugs, all opioids, synthetic opioids, heroin or stimulants, USA, 2010-2020. *Inj Prev*. 2024;0:1-11, at p. 5. E-pub ahead of print.

¹⁷⁵³ *Id.*, p. 91.

¹⁷⁵⁴ CDC, Data Brief 356, fn. 1735, above, at p. 4.

¹⁷⁵⁵ Bedson, “Risk of adverse events”, fn. 1732, above, at p. 908.

¹⁷⁵⁶ *Id.* at p. 913.

and clinical factors were statistically controlled There was no significant association between acetaminophen dose and regimen and suicide risk, suggesting that the observed effects may be specific to opioids.”¹⁷⁵⁷

- iii. In a *New England Journal of Medicine* article on opioids and suicide risk, Bohnert *et al.* note that “A reduction in the quantity of prescribed opioids may function as a ‘means restriction’ by reducing patients’ access to a lethal means of causing an intentional or unintentional opioid overdose. To this end, clinicians should ask about their patients’ access to opioids, including past prescriptions and medications prescribed to others in the same home. Taper protocols that involve small decreases in dosage over time are successful for reducing dosages and may actually reduce pain intensity. However, whether tapering changes the risk of either suicide or overdose is unknown.”¹⁷⁵⁸
- iv. As above, intentional opioid overdose, *i.e.* suicide, was nearly 4x more likely in patients prescribed long-term opioids at the highest doses (>50mg).¹⁷⁵⁹
- v. A Veterans Health Administration study examining the likelihood of death from overdose or suicide in veterans prescribed opioid analgesics in the early implementation period of VHA’s opioid safety initiative (2014-2016) found that “All patients exposed to opioids had an increased risk of death from overdose or suicide after starting or stopping treatment with opioids. Although patients treated with opioids for long periods (e.g., >400 days in our evaluation) had the highest hazard ratios after stopping treatment, even those treated for up to 30 days had a rise in the risk of death after treatment was stopped (hazard ratio of 1.4 for death from overdose after stopping opioid treatment and 1.7 for death from overdose or suicide). Those treated with opioids for 31-90 days had a hazard ratio of 2.4 for death from overdose after stopping opioid treatment (2.8 for death from overdose or suicide).”¹⁷⁶⁰ In other words, opioids increase the risk of overdose death in the initiation phase, the maintenance phase, and the discontinuation phase,

¹⁷⁵⁷ Ilgen MA, Bohnert AS, *et al.* Opioid Dose and Risk of Suicide. *Pain*. 2016 May; 157(5): 1079–1084. doi:10.1097/j.pain.0000000000000484, at p. 5.

¹⁷⁵⁸ Bohnert ASB, Ilgen MA. Understanding Links among Opioid Use, Overdose, and Suicide. *N Engl J Med*. 2019. doi:10.1056/nejmra1802148, at p. 76.

¹⁷⁵⁹ Bedson *et al.* “Risk of Adverse Events”, fn. 1732, above, at p. 913.

¹⁷⁶⁰ Oliva EM, *et al.* Associations between stopping prescriptions for opioids, length of opioid treatment, and overdose or suicide deaths in US veterans: Observational evaluation. *BMJ*. 2020;368:m283:1-10, at p. 6. The study “did not take into consideration the reasons or clinical intentions for stopping, or the speed of its execution.”

highlighting the lethality of these drugs at all stages of treatment. Further, risks increase with increasing dose and duration.¹⁷⁶¹

- f. Opioids are associated with more adverse medical outcomes and increased mortality and morbidity than non-opioid analgesics (NSAIDs),¹⁷⁶² contrary to the claim that morbidity and mortality of non-opioid medications (NSAIDs) for pain are comparable.¹⁷⁶³
- g. The opioid epidemic is also partly responsible for the spread of Hepatitis C, HIV and other infectious diseases across the country in recent years, as people who become addicted to prescription opioids, transition to injection drug use and share needles with others who are infected. For example, the outbreak of Hepatitis C and HIV in Scott County, Indiana in 2015, “resulted from inappropriate prescribing of opioid medications.”¹⁷⁶⁴
- h. Misuse and addiction
 - i. As discussed in this report, above, misuse of prescription opioids and addiction are significant problems throughout the United States; prescription opioids have been a major stepping stone for illicit opioid use and resulting harms; and over-prescribing contributes to population risk of opioid related harms.
 - ii. 11 million people misused prescription opioids in 2016, compared to the approximately 1 million people using heroin. In 2011, according to a CDC report, 11 million people reported nonmedical use of opioid analgesics. “Moreover, chronic nonmedical use of opioid analgesics (*i.e.* nonmedical use on 200 days or more in the past year) increased roughly 75% between 2002-2003 and 2009-2010. This increase means that on average in 2009-2010 there were nearly 1 million people in the U.S. with chronic nonmedical use of opioid analgesics.”¹⁷⁶⁵

¹⁷⁶¹ *Id.* at p. 6.

¹⁷⁶² Solomon DH, Rassen Ja, Glynn RJ, Lee J, Levin R, Schneeweiss S. The comparative safety of analgesics in older adults with arthritis. *Arch Intern Med.* 2010;170(22):1968-1976. doi:10.1001/archinternmed.2010.391, at p. 1968.

¹⁷⁶³ Tayeb BO, Barreiro AE, Bradshaw YS, Chui KKH, Carr DB. Durations of opioid, non-opioid drug, and behavioral clinical trials for chronic pain: Adequate or inadequate? *Pain Med (United States)*. 2016. doi:10.1093/PM/PNW245, at p. 2043.

¹⁷⁶⁴ Strathdee SA, Beyrer C. Threading the Needle — How to Stop the HIV Outbreak in Rural Indiana. *N Engl J Med.* 2015. doi:10.1056/NEJMp1507252, at p. 398.

¹⁷⁶⁵ United States Dep’t of Health and Human Servs. *Addressing Prescription Drug Abuse in the United States*. 1-36, at pp., 9-10, https://www.cdc.gov/drugoverdose/pdf/hhs_prescription_drug_abuse_report_09.2013.pdf.

- iii. Nearly 2 million (0.8%) of people in the United States are addicted to opioids based on estimates from the 2015 National Survey on Drug Use and Health (NSDUH).¹⁷⁶⁶
- iv. Even among cancer patients, the rates of opioid misuse and addiction is very high, with a recent study finding that 19% of cancer patients taking opioids for cancer pain develop nonmedical opioid use (i.e., misuse) within a median duration of 8 weeks after initial supportive care clinic consultation.¹⁷⁶⁷
- v. The opioid epidemic may be contributing to the risk of dementia. Evidence has shown that the longer term consequences of opioid use disorder include an 88% higher risk for developing Alzheimer's Disease/dementia within 1 year compared to those without OUD (aHR=1.88, 95% CI 1.74, 2.03) and a 211% higher risk for developing Alzheimer's Disease/dementia (aHR=3.11, 95% CI 2.63, 3.69) within 10 years.¹⁷⁶⁸

13. There is no doubt that a cause-and-effect relationship exists between the oversupply of prescription opioids and the opioid epidemic.

- i. Defense experts in this litigation have repeatedly and mistakenly claimed that the prescription opioid oversupply and the opioid epidemic are associated but not causally linked.¹⁷⁶⁹ Defendants' denial of

¹⁷⁶⁶ Han B, Compton WM, Blanco C, Crane E, Lee J, Jones CM. Prescription Opioid Use, Misuse, and Use Disorders in U.S. Adults: 2015 National Survey on Drug Use and Health. *Annals of Internal Medicine*. 2017;167(5):293-301. Epub 2017/08/02. doi: 10.7326/m17-0865. PubMed PMID: 28761945, at 293.

¹⁷⁶⁷ Yennurajalingam S, *et al.* Frequency of and factors associated with nonmedical opioid use behavior among patients with cancer receiving opioids for cancer pain. *JAMA Oncol*. 2021;1-8. Doi:10.1001/jamaoncol.2020.6789, at 1.

¹⁷⁶⁸ Qeadan F, *et al.* Exploring the association between opioid use disorder and Alzheimer's disease and dementia among a national sample of the US population. *Journal of Alzheimer's Disease*. 2023;96(1):229-244, at p. 229 and Table 2. While the authors acknowledge that the exact underlying mechanisms between OUD and the onset of dementia remain to be fully elucidated, chronic opioid use and abuse has been associated with brain inflammation and prolonged periods of hypoxia which are in turn associated with the onset of dementia.

¹⁷⁶⁹ See, e.g., Expert Report of Rob Lyerla. *In re: Nat'l Prescription Opiate Litig.*, No. 1:17-MD-2804 (May 10, 2019) ("Plaintiffs' experts purport to demonstrate a causal relationship between opioid use and opioid misuse and mortality. However, the data they use are insufficient to support their conclusions."), Expert Report of Stephanie W. Colston, *City of Huntington, West Virginia et al. v. AmerisourceBergen Drug Corporation et al.*, Case No. 3:17-01362 (August 27, 2020) ("A substantial body of empirical evidence documents that prescription opioids are not the causal culprit of the opioids abuse crisis. These studies document that the root causes of the opioid abuse crisis are considerably broader than supply alone and, in addition, the studies demonstrate that supply-only responses to the opioids abuse crisis have had deleterious public health and safety consequences."), Expert Report of Peggy Compton, *City of Huntington, West Virginia et al. v. AmerisourceBergen Drug Corporation et al.*, Case No. 3:17-01362 (August 27, 2020) ("persons with opioid use disorder will seek opioids from many sources, including a physician, however this should not be interpreted to mean that the prescribed opioid is causally related to the development of addiction."), and Expert Report of Kevin M. Murphy, *City of Huntington, West Virginia et al. v.*

causation parallels the history of smoking and cancer. For much of the 20th century, scientific literature had reported an “association” between exposure to cigarettes and the occurrence of lung cancer, that is, lung cancer was found to have occurred more frequently among smokers. However, cigarette manufacturers denied that their products had “caused” the increased number of lung cancer cases and relied upon publications that attributed the association to other factors.

- ii. In 1956, the noted British epidemiologists, Sir Richard Doll and Sir Austin Bradford Hill published an influential study of smoking and lung cancer among physicians in Britain. This article recounted and rejected alternative explanations for the increase in lung cancer, *e.g.*, “that smoking does not produce cancer in a person in whom cancer would not otherwise have occurred at all, but merely determines the primary site of a growth that is destined to appear in some part of the body,”¹⁷⁷⁰ and that “atmospheric pollution” might explain the increased risk.¹⁷⁷¹
- iii. Doll and Hill observed a higher mortality in smokers than in non-smokers, a higher mortality in heavy smokers than in light smokers, and a higher mortality in those who continued to smoke than in those who gave it up.¹⁷⁷² In 1964, their study became part of the data set that resulted in the 1964 Report of the United States Surgeon General that “cigarette smoking is causally related to lung cancer in men; the magnitude of the effect of cigarette smoking far outweighs other factors. The data for women, though less extensive, point in the same direction.”¹⁷⁷³
- iv. In 1965, one of the authors of that landmark smoking study, Sir Austin Bradford Hill, published an essay that has become the framework for answering the question of when a statistical finding of association meets threshold criteria for causation: “What aspects of that association should we especially consider before deciding that the most likely interpretation of it is causation?”¹⁷⁷⁴ The “Bradford Hill factors,” as they have become known, are generally accepted in the scientific literature, as the leading methodology to determine whether there is a

AmerisourceBergen Drug Corporation et al., Case No. 3:17-01362 (August 27, 2020) (“An association between opioid supply and opioid mortality (or other opioid-related harms) does not establish a causal link.”).

¹⁷⁷⁰ Doll and Hill. Lung Cancer and Other Causes of Death in Relation to Smoking: A Second Report on the Mortality of British Doctors. *British Medical Journal*, 1956, 1071-1081, at 1077.

¹⁷⁷¹ *Id.* at 1078.

¹⁷⁷² *Id.* at 1081.

¹⁷⁷³ Report of the Advisory Committee to the Surgeon General, *Smoking and Health*. Public Health Service Publication No. 1103, January 1964. <https://profiles.nlm.nih.gov/spotlight/nn/catalog.nlm.nlmuid-101584932X204-doc>, at 31.

¹⁷⁷⁴ Hill AB, The Environment and Disease, fn. 105, above.

causal relationship between exposure to a risk factor and the occurrence of disease.¹⁷⁷⁵

- v. The factors cited by Bradford Hill to determine whether an association is causal are as follows: (1) Strength of the association, (2) Consistency, (3) Specificity (4) Temporality, (5) Dose-response relationship, sometimes called “biological gradient,” (6) Plausibility (7) Coherence, (8) Experiment,¹⁷⁷⁶ and (9) Analogy. These factors are a guide, not a checklist: “There is no formula or algorithm that can be used to assess whether a causal inference is appropriate based on these guidelines. One or more factors may be absent even when a true causal relationship exists. Similarly, the existence of some factors does not ensure that a causal relationship exists. Drawing causal inferences after finding an association and considering these factors requires judgment and searching analysis, based on biology, of why a factor or factors may be absent despite a causal relationship, and vice versa. Although the drawing of causal inferences is informed by scientific expertise, it is not a determination that is made by using an objective or algorithmic methodology. These guidelines reflect criteria proposed by the U.S. Surgeon General in 1964 in assessing the relationship between smoking and lung cancer and expanded upon by Sir Austin Bradford Hill in 1965 and are often referred to as the Hill criteria or Hill factors.”¹⁷⁷⁷
- vi. As summarized below, the sources cited in this Report provide more than sufficient evidence that there is a causal relationship between prescription opioids, their oversupply, and the various harms described, based on this generally accepted methodology. There are numerous parallels to the relationship between smoking and lung cancer, including strength of association, dose-response relationship, temporality, and consistency across multiple studies. An additional

¹⁷⁷⁵ I am aware that Judge Polster cited the Bradford Hill factors, and the Federal Judicial Center’s *Reference Manual on Scientific Evidence* that lists those factors, in his Order denying the MDL Defendants’ motion to exclude my opinions. See Order Denying Defendants’ Motion to Exclude Expert Testimony of Katherine Keyes, Anna Lembke and Jonathan Gruber re the “Gateway Hypothesis” of Causation, *In re: Nat’l Prescription Opiate Litig.*, No. 1:17-MD-2804, 2019 WL 4043943 (N.D. Ohio Aug. 26, 2019), at 11-12.

¹⁷⁷⁶ The factor of “Experiment” is referred to as “Cessation of Exposure” in the set of “Hill factors” provided by the Federal Judicial Center, *Reference Manual on Scientific Evidence* (3rd edition, 2011), which states: “If an agent is a cause of a disease, then one would expect that cessation of exposure to that agent ordinarily would reduce the risk of the disease. This has been the case, for example, with *cigarette smoking and lung cancer*. . . . [W]hen such data are available and eliminating exposure reduces the incidence of disease, this factor strongly supports a causal relationship.” (*Id.* at 605; emphasis added). This formulation closely matches Bradford Hill’s description of the “Experiment” factor: “Occasionally it is possible to appeal to experimental, or semi-experimental, evidence. For example, because of an observed association *some preventive action is taken. Does it in fact prevent?* The dust in the workshop is reduced, lubricating oils are changed, *persons stop smoking cigarettes. Is the frequency of the associated events affected? Here the strongest support for the causation hypothesis may be revealed.*” Hill AB, The Environment and Disease, fn. 105, above, at 298-299 (emphasis added).

¹⁷⁷⁷ Federal Judicial Center, *Reference Manual on Scientific Evidence*, 3rd edition, 2011, at 599-600.

parallel is that widespread increased access to and promotion of cigarettes gave rise to more young people starting smoking and fewer users quitting; as well as contributed to greater consumption among users across the United States.¹⁷⁷⁸

- vii. In evaluating the evidence, the factors of strength of association, consistency, temporality, dose-response, biological plausibility, and experiment/cessation of exposure are most important.
- viii. Bradford Hill's article states as follows: "(1) *Strength*. First upon my list I would put the strength of the association."¹⁷⁷⁹ Regarding this factor, the *Reference Manual on Scientific Evidence* states: "The relative risk is one of the cornerstones for causal inferences. Relative risk measures the strength of the association. The higher the relative risk, the greater the likelihood that the relationship is causal. For cigarette smoking, for example, the estimated relative risk for lung cancer is very high, about 10. That is, the risk of lung cancer in smokers is approximately 10 times the risk in nonsmokers. A relative risk of 10, as seen with smoking and lung cancer, is so high that it is extremely difficult to imagine any bias or confounding factor that might account for it. The higher the relative risk, the stronger the association and the lower the chance that the effect is spurious."¹⁷⁸⁰
- ix. A standard textbook in epidemiology, written by a Professor at the Harvard School of Public Health, describes ratios of between 3.0 and 10.0 as "strong," and a ratio of over 10.0 as "infinite," meaning that it is extremely unlikely to be explained by any confounding or bias.¹⁷⁸¹
- x. There are two complementary and mutually reinforcing perspectives to view the strength of association between prescription opioids and adverse outcomes such as addiction and mortality. First is the association found in specific exposed populations; second is the association found on a national level, as a result of prescription opioid promotion, sale, and distribution. These are addressed below.
- xi. Strength of association in specific exposed populations: The evidence in this case shows "strong" and even "infinite" ratios of death and disease among specific populations exposed to prescription opioids, compared to unexposed subjects. The peer-reviewed Edlund study discussed at Section §C.4.f., analyzed claims and prescription information from two large healthcare databases. The study reported

¹⁷⁷⁸ U.S. Surgeon General, *Preventing Tobacco Use Among Youth and Young Adults*. 2012, at Chapter 5, p. 487.

¹⁷⁷⁹ Hill AB, *The Environment and Disease*, fn. 105, above, at 295. (emphasis in original).

¹⁷⁸⁰ Federal Judicial Center, *Reference Manual on Scientific Evidence*, 3rd edition, 2011, at 602. *See also*, 1964 Surgeon General's report at Table 2, p. 29, citing 10.8x higher rate of lung cancer among smokers compared to non-smokers.

¹⁷⁸¹ *See, e.g.*, Monson, Richard. *Occupational Epidemiology*. CRC Press. (2nd edition, 1990), at 88.

exceptionally high hazard ratios (HRs) of 14.92, 28.69, and 122.45 for diagnosis of opioid addiction among subjects with low, moderate, and high-dose chronic (> 90 days) exposure to prescription opioids, respectively, compared to subjects with no exposure to prescription opioids. All of these ratios exceed the relative risk of 10 for smoking and lung cancer, and also exceed a threshold for “infinite” association. Indeed, for patients on prescription opioids equivalent to 120 mg of morphine daily for three months or more, the risk of becoming addicted to opioids as a result of that prescription is more than ten times the risk of developing lung cancer as a result of smoking cigarettes. The data therefore provide exceptionally strong support for causality of opioid addiction by chronic exposure to prescription opioids.

- xii. Strong associations are also demonstrated between prescription opioid exposure and fatal/nonfatal overdose, among specific populations. The peer-reviewed study by Dunn, discussed in Section §C.12.c. of this Report, reported HR of 8.87 for opioid overdose, including fatal and non-fatal, among members of a Washington State healthcare organization who were exposed to prescription opioids > 100 MME per day, compared to subjects without prescription opioid exposure; the Bohnert study, also discussed at Section §C.12.c., showed a similar HR of 7.19 for fatal overdose among Veterans Health Administration patients exposed to > 100 MME per day, compared to subjects with < 20 MME per day. Both of these HRs are toward the upper end of the “strong” category of association. Defense experts fail to address the importance of these strong associations that support causation.
- xiii. Analogous increased rates of prescription opioid overdose have been demonstrated in state and national data sets since the oversupply began in the late 1990s. “From 1999 to 2007 in Ohio, there were increases of 304 percent and 325 percent, respectively in the unintentional drug poisoning death rate and total grams of prescription opioids distributed per 100,000 population.”¹⁷⁸² Based on these data, the Ohio Department of Health concluded, “There is a *strong relationship* between increases in sales of prescription opioids and fatal unintentional drug poisoning rates.”¹⁷⁸³ This “strong” relationship was enabled by widespread distribution, resulting in over a three-fold increase in per capita prescriptions. Similar increased prescription opioid sales, distribution, mortality and hospitalization occurred nationally, as shown in Section §C.3.b of this Report. As noted by CDC authors, “Increased use of

¹⁷⁸² Ohio Department of Health, Violence and Injury Prevention Program. “Epidemic of Prescription Drug Overdose in Ohio, 1999-2009,” July 18, 2018, at 2. https://odh.ohio.gov/wps/wcm/connect/gov/5a0bbf8a-8d88-49e5-bd6c-56ca28c2104c/Epidemic_of_Prescription_Drug_Overdose_Ohio_Report.pdf

¹⁷⁸³ *Id.*, (emphasis added).

OPR [Opioid pain Relievers] has contributed to the overall increases in rates of overdose death and nonmedical use, and variation among states in OPR sales probably contributes to state variation in these outcomes.”¹⁷⁸⁴

- xiv. There is essentially uniform agreement in the published literature that promotion and widespread distribution of prescription opioids resulted in the oversupply that gave rise to the epidemic of addiction and mortality. As noted previously, the NASEM and ASPPH reports, both highly reputable and respected sources, identified aggressive marketing, including misleading promotion by some, as well as distribution throughout the country, as key factors contributing to the epidemic.¹⁷⁸⁵
- xv. (2) *Consistency* refers to whether similar findings have been “repeatedly observed by different persons, in different places, circumstances and times.”¹⁷⁸⁶ As with the factor of “Strength of Association,” *Consistency* is also apparent in specific study populations as well as state and national data sets. Numerous references cited in this Report provide consistency of the observed relationship between prescription opioids and the adverse outcomes of opioid addiction and overdose in particular populations.
- xvi. Consistent with the Edlund study, Papadomanolakis-Pakis was an incidence study that reported risk of opioid addiction among Ontario, Canada residents whose records were part of a healthcare database; HRs in that study increased with duration of the initial opioid prescription.¹⁷⁸⁷ As discussed in Section §C.8.b of this Report, the Vowles systematic review found elevated risks of addiction and misuse in 38 studies of chronic pain patients exposed to prescription opioids, and the Boscarino study reported similarly elevated risks.
- xvii. The relationship between increased prescription *opioid sales* and increased drug overdose mortality has also been demonstrated repeatedly, and consistently. As noted above in the discussion of

¹⁷⁸⁴ Paulozzi, *et al.*, Vital Signs: Overdoses of Prescription Opioid Pain Relievers --- United States, 1999—2008. *MMWR*, November 4, 2011 / 60(43):1487-1492. *See also*, Walley, Alexander Y., *et al.* “The contribution of prescribed and illicit opioids to fatal overdoses in Massachusetts, 2013-2015.” *Public Health Reports* 134.6 (2019): 667-674., <https://doi.org/10.1177/0033354919878429>, at 667. “In the United States in the 1990s and early 2000s, annual increases in opioid-related overdose deaths and entries into treatment for opioid addiction paralleled increases in prescriptions of opioid medications for pain. *This correlation appears to have been causal*, as the expansion of opioid prescribing for pain led to more persons overdosing on opioids and more persons seeking treatment for opioid use disorder.” (emphasis added).

¹⁷⁸⁵ *See* Section §C.2.j. of this Report, above.

¹⁷⁸⁶ Hill AB, The Environment and Disease, fn. 105, above, at 296. (emphasis in original)

¹⁷⁸⁷ Papadomanolakis-Pakis, N, *et al.* Prescription opioid characteristics at initiation for non-cancer pain and risk of treated opioid use disorder: A population-based study. *Drug and Alcohol Dependence*. 2021:221:1-9.

Strength of Association, the Ohio Department of Health reported, based on data from 1999-2009, “There is a strong relationship between increases in sales of prescription opioids and fatal unintentional drug poisoning rates.”¹⁷⁸⁸ The CDC data showed a similar relationship at the national level.¹⁷⁸⁹ These similar findings support the Hill factor of Consistency, as well as Strength of Association.

- xviii. (3) *Temporality*: “A temporal, or chronological, relationship must exist for causation to exist. If an exposure causes disease, the exposure must occur before the disease develops. If the exposure occurs after the disease develops, it cannot have caused the disease.” *Temporality* is established in both specific study populations and national data sets.
- xix. The incidence studies (Edlund, Papadomanolakis-Pakis) cited above demonstrate that diagnoses of opioid addiction followed exposure to prescription opioids, since the study designs excluded subjects with opioid addiction prior to the beginning of the study period. Temporality was also shown in a study reporting that “exposure to opioids through a dental clinician in a population of opioid naïve patients was associated with higher use of opioids at 90 to 365 days later and subsequent diagnoses associated with opioid abuse or overdose compared with controls. ... [T]he higher probability of abuse diagnoses in the exposed cohort suggests that many of the repeated opioid prescriptions in this cohort were related to substance abuse.”¹⁷⁹⁰ The authors reported subsequent opioid prescriptions at 90 to 365 days among 6.9% of the dental patients who received opioids, compared to only 0.1% of those treated with non-opioids.¹⁷⁹¹
- xx. In state and national data, a temporal relationship also has been documented between increased distribution of prescription opioids and increased mortality, in the CDC and state-specific data, as referenced above and in Appendix III.¹⁷⁹²

¹⁷⁸⁸ Ohio Department of Health, Violence and Injury Prevention Program. “Epidemic of Prescription Drug Overdose in Ohio, 1999-2009,” July 18, 2018, at p.2. https://odh.ohio.gov/wps/wcm/connect/gov/5a0bbf8a-8d88-49e5-bd6c-56ca28c2104c/Epidemic_of_Prescription_Drug_Overdose_Ohio_Report.pdf

¹⁷⁸⁹ See data and graph at Section §C.3.b above.

¹⁷⁹⁰ Schroeder, *et al.*, Association of Opioid Prescriptions from Dental Clinicians for US Adolescents and Young Adults with Subsequent Opioid Use and Abuse. *JAMA Internal Medicine* 2018; doi:10.1001/jamainternmed.2018.5419, at E5.

¹⁷⁹¹ *Id.* at E3-E4.

¹⁷⁹² Similarly, in the 1964 Surgeon General’s Advisory Committee Report on Smoking and Health, the increase in lung cancer was observed in the context of large increases in exposure to cigarettes: “Nearly 70 million people in the United States consume tobacco regularly. Cigarette consumption in the United States has increased markedly since the turn of the Century, when per capita consumption was less than 50 cigarettes per year,” and cigarette consumption rose from 138 per person in 1910 to a “peak of 3,986 [per person] in 1961.” 1964 Surgeon General’s

- xxi. *Temporality* also exists with respect to the Gateway Effect, as documented by undisputed evidence that increased use and misuse of prescription opioids preceded the second and third waves of the epidemic involving the transition from prescription opioids to heroin and fentanyl. Muhuri and others documented the fact that 70-80% of recent heroin users had previously used prescription opioids.¹⁷⁹³ McCabe, Lankenau and Mars all demonstrated that this transition occurred after both medical use (pursuant to a doctor's prescription) and nonmedical use (outside the parameters of a doctor's prescription).¹⁷⁹⁴
- xxii. (4) *Dose-response*: "[I]f the association is one which can reveal a biological gradient, or dose-response curve, then we should look most carefully for such evidence. For instance, the fact that the death rate from cancer of the lung rises linearly with the number of cigarettes smoked daily, adds a very great deal to the simpler evidence that cigarette smokers have a higher death rate than non-smokers."¹⁷⁹⁵
- xxiii. Numerous studies cited above provide clear and convincing evidence of a dose-response relationship, including but not limited to Edlund, Dunn, Bohnert, and Papadomanolakis-Pakis, all of which found increased risk of either opioid addiction or overdose with greater exposure to prescription opioids.
- xxiv. An analogous result is found with regard to the "Gateway Effect," in that more frequent misuse of prescription opioids is associated with a higher rate of transition to heroin.¹⁷⁹⁶ A CDC publication similarly reported, "Drug abuse and overdose rates increased with longer use,"¹⁷⁹⁷ and another CDC publication simply stated: "Higher Dosage, Higher Risk,"¹⁷⁹⁸ neatly summarizing the evidence of a dose-response relationship between prescription opioids and overdose.

Report, fn.1773, above, at 26. This stark increase in tobacco consumption has a parallel in the large-scale increased distribution of opioids between the 1990s and 2012, with only a modest decline since that time.

¹⁷⁹³ Report, above, at §C.9.h.

¹⁷⁹⁴ Report, above, at §C.9.h.

¹⁷⁹⁵ Hill AB, The Environment and Disease, fn. 105, above, at p. 298. (emphasis in original). See also, 1964 Surgeon General's Report, fn. 1773, above, at p. 35: "The death rates increase with the amount smoked."

¹⁷⁹⁶ Jones CM, Heroin use and heroin use risk behaviors among nonmedical users of prescription opioid pain relievers – United States, 2002-2004 and 2008-2010. *Drug Alcohol Depend.* 2013;132(1-2):95-100, at 95.

¹⁷⁹⁷ Paulozzi LJ, et al. Risk of Adverse Health Outcomes with Increasing Duration and Regularity of Opioid Therapy. *J Am Board Fam Med.* 2014 ; 27(3): 329–338, at p. 329. doi:10.3122/jabfm.2014.03.130290, at 329.

¹⁷⁹⁸ Centers for Disease Control and Prevention, Calculating Total Daily Dose of Opioids for Safer Dosage. https://www.cdc.gov/drugoverdose/pdf/calculating_total_daily_dose-a.pdf, at 1.

- xxv. Dose-response was also found in a study reporting that odds of overdose were significantly greater with increasing amounts of opioids dispensed to family members (>0-<50 morphine milligram equivalents per day: OR, 2.71 [95% CI, 2.42-3.03]; 50-<90 morphine milligram equivalents per day: OR, 7.80 [95% CI, 3.63-16.78]; ≥90 morphine milligram equivalents per day: OR, 15.08 [95% CI, 8.66-26.27]).¹⁷⁹⁹ These findings are of particular importance in demonstrating the causal relationship between oversupply and opioid overdose, since overprescribing provides a source for excess opioid pills that are diverted from the original recipient to family members who suffer the adverse effects.
- xxvi. *Dose-response* has similarly been shown with respect to promotion, sale and distribution of opioids. In the Hadland studies described previously, the authors explicitly stated that their data showed a dose-response relationship between opioid manufacturers' marketing and the occurrence of opioid prescribing, with each additional industry-sponsored meal associated with additional opioid prescribing.¹⁸⁰⁰
- xxvii. ARCOS data on opioid sales also strongly support Dose-response on a population scale. "Death rates from opioids soared in the towns, cities and counties that were saturated with billions of prescription pain pills from 2006 through 2012, according to government death data and a previously undisclosed database of opioid shipments made public this week. ... The national death rate from opioids was 4.6 deaths per 100,000 residents. But the *counties that had the most pills distributed per person experienced more than three times that rate on average.*"¹⁸⁰¹ My colleague at Stanford, Keith Humphreys, who served as a drug policy adviser to the George W. Bush and Obama administrations, "said the *correlation of opioid deaths and pain pill distribution could be expected.* 'These horrible death rates should not surprise anyone,' Humphreys said. '*The supply of drugs matters enormously no matter what else we try to do. When there's a flood of addictive drugs, lots of people end up being harmed.*'"¹⁸⁰²
- xxviii. A further example of *dose-response* at the population level is found in a 2019 study by Ghertner, documenting the relationship between opioid

¹⁷⁹⁹ Khan, *et al.*, Association of Opioid Overdose with Opioid Prescriptions to Family Members. JAMA Internal Medicine (2019), doi:10.1001/jamainternmed.2019.1064, at E-3.

¹⁸⁰⁰ Hadland SE, *et al.* In Reply. JAMA. 2018;178(10):1426-1427 at 1426.

¹⁸⁰¹ Horwitz, *et al.* Opioid death rates soared in communities where pain pills flowed. (July 17, 2019) https://www.washingtonpost.com/investigations/opioid-death-rates-soared-in-communities-where-pain-pills-flowed/2019/07/17/f3595da4-a8a4-11e9-a3a6-ab670962db05_story.html, at 1 (emphasis added).

¹⁸⁰² *Id.* at 4 (emphasis added). To the best of my knowledge, Professor Humphreys is not a retained witness in any opioid litigation.

sales (ARCOS data) with county-level opioid-related hospitalization rates. Ghertner reported that there was a 9% increase in opioid-related hospitalizations for each one morphine kilogram equivalent increase in opioid sales.¹⁸⁰³ This study further documents that the *Dose-response* factor is operative at both the personal and population levels, with respect to individual exposures as well as widespread promotion and distribution to the nation as a whole.

xxix. (6) *Plausibility*: “Biological plausibility is not an easy criterion to use and depends upon existing knowledge about the mechanisms by which the disease develops. When biological plausibility exists, it lends credence to an inference of causality.”¹⁸⁰⁴

xxx. In this case, biological plausibility of prescription opioids as the cause of the various harms described in this Report has been established by the evidence detailed in Sections §C.1 and §C.2, above. In summary, the molecular similarity between prescription opioids and heroin, the impact of these molecules on the dopamine system and the development of the disease of addiction, and their effects on respiratory suppression (slowed breathing) and bradycardia (lowered heart rate) as the cause of overdose death, are well-documented and established. It is similarly well-known that the phenomenon of tolerance is common, requiring prescription opioid users to increase the dose to achieve the same effect, thereby increasing the risk in accordance with the dose-response effects documented above.

xxxi. *Experiment*: As mentioned above, this factor refers to the effects of prevention or cessation of exposure in reducing disease. CDC data show that “Opioid prescribing has declined substantially across the United States between 2014 and 2017,”¹⁸⁰⁵ and that prescription opioid-involved overdose death rates decreased by 13.5% from 2017-2018.¹⁸⁰⁶ Also, a recent Continuing Medical Education publication stated, “Patients with opioid problems may have extended periods of abstinence and usually do well. However, there is a chronic risk of accidental overdose, trauma, suicide, and infectious diseases. *The risk decreases with abstinence from opioids.*”¹⁸⁰⁷

xxxii. Summary: According to the generally accepted methods described above, it is clear that widespread sale and distribution of prescription

¹⁸⁰³ Ghertner, “U.S. county prevalence of retail prescription opioid sales”, fn. 1685, above.

¹⁸⁰⁴ Federal Judicial Center, *Reference Manual on Scientific Evidence*, 3rd edition, 2011, at 604.

¹⁸⁰⁵ Kuehn B. (2019). Declining Opioid Prescriptions. *JAMA*, 321(8), 736. <https://doi.org/10.1001/jama.2019.0647>

¹⁸⁰⁶ Centers for Disease Control and Prevention, Press Release, New Data Show Significant Changes in Drug Overdose Deaths (March 18, 2020) <https://www.cdc.gov/media/releases/2020/p0318-data-show-changes-overdose-deaths.html>

¹⁸⁰⁷ Dydyk, A. M., Jain, N. K., & Gupta, M. (2020). Opioid Use Disorder. <https://www.ncbi.nlm.nih.gov/books/NBK553166>, at 2 (emphasis added).

opioids have resulted in exposures that are causally related to the epidemics of fatal and non-fatal opioid overdose, opioid addiction, and transition to illicit opioid use.

14. For the reasons explained, the Pharmaceutical Opioid Industry bears responsibility for the misrepresentation of safety and efficacy, the ubiquitous distribution of prescription opioids, and the unchecked dispensing of prescription opioids, which resulted in the ongoing epidemic. To the extent that other factors contributed, those conditions were exploited by the Industry to increase the extent of harm.

- a. As I wrote in my book, *Drug Dealer, MD*,¹⁸⁰⁸ doctors were “duped” by the myths that the risk of addiction to prescription opioids was “rare,” and that the drugs were beneficial for chronic pain. I also wrote at that time, and I continue to hold the opinion, that others had some responsibility for the opioid epidemic.
- b. The Food and Drug Administration (FDA) is an agency within the U.S. Department of Health and Human Services responsible for assuring the safety, effectiveness, and quality of medical drugs. It is responsible for approving drugs before they reach the market, and monitoring the safety and marketing of those drugs after they are publicly available. In my book, *Drug Dealer, MD*, I assigned some responsibility for the prescription drug epidemic to the FDA, and to the Defendants for efforts to influence the FDA.¹⁸⁰⁹
- c. The Toyota-ization of Medicine
 - i. The majority of doctors today work in large integrated health care systems. During the 1990s and 2000s, there occurred a mass migration of doctors out of private practice and into managed care organizations. In 2002, 70% of U.S. physician practices were physician-owned. By 2008, more than 50% of U.S. physician practices were owned and operated by hospitals or integrated health delivery systems, and that number continues to rise.¹⁸¹⁰
 - ii. The migration of doctors into integrated health care systems (hospital factories) has transformed medical treatment. Doctors work much less autonomously. Treatment options are often dictated by hospital administrators, guidelines (*see* Joint Commission, §C.4.m, above), and third-party payers (health insurance companies). The result is that

¹⁸⁰⁸ Lembke, “*Drug Dealer, MD*,” fn. 3, above.

¹⁸⁰⁹ Lembke, “*Drug Dealer, MD*,” fn. 3, above; Fauber J. FDA and Pharma: Emails Raise Pay-for-Play Concerns. *Sentinal/MedPage Today*. October 7, 2003, *see* <http://www.medpagetoday.com/PainManagement/PainManagement/42103>, at p. 1.

¹⁸¹⁰ Kocher R, Sahni N. Hospitals ‘ Race to Employ Physicians — The Logic Behind a Money Losing Proposition. *N Engl J Med*. 2011;1790-1793, at p. 1791.

doctors experience enormous pressure to get patients in and out quickly, to palliate pain, and to have “satisfied customers.” This too has contributed to the problem of overprescribing.¹⁸¹¹

- iii. These structural factors opened the doors, but the aggressive misrepresentation of risks and benefits took advantage of these conditions to maximize sales and maximize harm.
- d. I have also written, in *Drug Dealer, MD*, about the manipulative behaviors of patients in attempting to obtain opioid drugs from their doctors. These behaviors are not surprising; in fact, they are diagnostic of the disease of addiction, whether the drug is OxyContin, or Opana, or heroin. In my opinion, the Pharmaceutical Opioid Industry has attempted to blame victims of the disease of addiction for the epidemic resulting from their own misleading statements regarding their dangerously addictive drugs, while at the same time promoting the false message that patients taking these drugs for pain under a doctor’s prescription have little or no risk of addiction or overdose.
- e. An article published in *Science* in 2018 by Jalal, *et al.*, “Changing Dynamics of the Drug Overdose Epidemic in the United States from 1979-2016,”¹⁸¹² suggests that mortality data from numerous “drug-specific subepidemics” can be fitted to a smooth exponential curve during that time period. However, the authors note the “paradox” presented by these results, since the data combine mortality associated with subepidemics as disparate as heroin and fentanyl deaths in the northeastern United States with methamphetamines in the southwestern states.¹⁸¹³ Accordingly, an after-the-fact fitting of 38 years of combined data to a smooth curve does not obviate the need to understand each subepidemic on its own terms. In the case of prescription opioids, factors relevant to that epidemic have been addressed throughout this report, and are summarized as follows:
 - i. The apparent continuity of the overdose mortality rate curve in the Jalal *et al.* article, on closer inspection, shows a definitive rise above the smooth curve between 2001 and 2010, corresponding to the prescription opioid epidemic.¹⁸¹⁴
 - ii. This is further affirmed in Jalal’s most recent paper on the subject which acknowledged the likely causal role of prescription opioids in rising overdose mortality, under the heading, “**What is causing the exponential growth trajectory,**” stating that: “Over the past forty years, the dominant opioids have transitioned from crude plant-based drugs (heroin) to *pharmaceutical grade semisynthetic drugs*

¹⁸¹¹ Lembke A. Why Doctors Prescribe Opioids to Known Opioid Abusers. *N Engl J Med*. 2012;367(17):1580-1581.

¹⁸¹² Jalal H, Buchanich JM, Roberts MS, Balmert LC, Zhang K, Burke DS. Changing dynamics of the drug overdose epidemic in the United States from 1979 through 2016. *Science*. 2018. doi:10.1126/science.aau1184.

¹⁸¹³ *Id.* at p. 1.

¹⁸¹⁴ *Id.*

(oxycodone) to fully synthetic drugs (fentanyl and its derivatives). With these improvements in synthesis have come *improvements in purity, lower prices, and increased potency*. Conventional market forces may be at play, with *lower costs in product leading to expanding markets, increased use, and greater demand*. Improved technologies for communications and transport may also be altering the economics of drug use.”¹⁸¹⁵ In other words, Burke and Jalal are explicit that prescription opioids are a *cause* of the exponential increase in overdose mortality, and that price and availability are key drivers.

- iii. A study by Segel *et al.* demonstrates that the prescription opioid epidemic that incited the broader opioid epidemic, has also contributed to the fourth wave of the epidemic involving a rise in sedative and stimulant overdose deaths.¹⁸¹⁶
- iv. The problem of addiction more broadly in society and culture today does not negate the significant role of opioids manufacturers and distributors in causing this epidemic. The misrepresentations of risks and benefits and the oversupply of prescription opioids through the distribution chain were essential contributing factors to the resulting epidemic.
- v. Although forces may be operative to accelerate demand, such as despair, loss of purpose, and dissolution of communities, studies show that the ‘push’ of increased access to opioids has played a bigger role than the ‘pull’ of despair.¹⁸¹⁷
- vi. Oversupply of prescription opioids is associated with increased opioid-related mortality. Approximately 86 billion oxycodone and hydrocodone pills were delivered to US pharmacies from 2006 to 2013 and per capita pill volume (“PCPV”) has been positively associated with opioid-related deaths (“ORDs”), so that “each one-pill increase in PCPV was associated with 0.20 additional ORDs within the following three years.”¹⁸¹⁸ Griffith *et al.* further found that “even after accounting for various confounding factors, counties with particularly high PCPV experienced substantially more (16,436) ORDs than counties with

¹⁸¹⁵ Burke DS, Jalal H. Reply Commentary by Jalal and Burke. *International Journal of Drug Policy*. 2022;104:103674: 1-5, at p. 4. (emphasis added)

¹⁸¹⁶ Segel, “Persistence and Pervasiveness”, fn. 1615, above, at p. 1.

¹⁸¹⁷ Ruhm, *et al.*, “Deaths of Despair,” fn. 1681, above.

¹⁸¹⁸ Griffith KN, *et al.* Implications of county-level variation in US opioid distribution. *Drug and Alcohol Dependence*. 2021;219:1-7, at p.3.

below-median PCPV. On a national level, these excess deaths equate to approximately 11.1% of all ORDs recorded from 2006 to 2013”.¹⁸¹⁹

- vii. The harms of the opioid epidemic are urgent and ongoing. According to the Stanford-*Lancet* Commission: “Large numbers of US and Canadian people are still becoming addicted to prescription opioids each year, and most of those who die from heroin and fentanyl overdoses are previous or current users of prescription opioids.”¹⁸²⁰ The Commission’s opioid crisis model estimates that, in the absence of any intervention, an additional 1,220,000 fatal opioid overdoses will occur in the US between 2020 and 2029.¹⁸²¹

15. Ending the epidemic of opioid addiction, dependence, and death will require significant investment of resources. An effective strategy will be multifaceted, and will accomplish the following: prevent new cases of addiction, dependence, and death (primary prevention), limit progression of harm (secondary prevention), and treat existing cases (treatment). These changes will require curbing opioid prescribing, re-educating patients and health care providers, creating de-prescribing clinics, promoting naloxone and other harm-reduction strategies, and building an enduring medical infrastructure to treat addiction.

- a. Primary prevention: Preventing new cases of the disease by limiting access to opioids, re-educating prescribers, and rebuilding communities devastated by the epidemic.
 - i. Opioids should not be prescribed as first line treatment for most forms of pain. Exceptions include cases of severe tissue injury, peri-operatively when multimodal analgesia is insufficient, and as palliative/end of life care.
 - A. For acute pain, the CDC guidelines recommend no more than 3 to 7 days of opioid treatment. Even within this general guideline, it is important to limit both the dose and frequency of administration of opioid drugs during the 3-7 day window, to minimize the increase in long-term use that has been documented following higher doses of opioids for acute pain, and to limit the diversion of unused pills.
 - B. First line treatment for pain should include non-opioid medications and non-medication treatment for pain (non-opioid medications, physical therapy, psychotherapy). The

¹⁸¹⁹ *Id.* at p. 4.

¹⁸²⁰ Stanford-*Lancet* Commission, fn 17, above, at p. 5.

¹⁸²¹ Stanford-*Lancet* Commission, fn 17, above, at p. 12.

Lembke Report

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Exhibits to this Report:

Attached as Exhibit A is a copy of my current curriculum vitae and a list of all publications authored by me in the past 10 years.

Attached as Exhibit B is a list of data or other information considered by me in forming the opinions expressed herein.

Attached as Exhibit C is a statement of my compensation for services performed in this case.

Attached as Exhibit D is a list of all cases in which I have testified as an expert at trial or by deposition during the past four years.

Pursuant to 28 U.S.C. S 1746, I declare under penalty of perjury that the foregoing is true and correct.

Executed on: April 15, 2024

A handwritten signature in cursive script, appearing to read 'Anna Lembke', written over a horizontal line.

Anna Lembke, M.D.

Lembke Report

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Anna Lembke, M.D. Report

APPENDIX III

Case Specific Data: Tarrant County, Texas

Appendix III: Case specific data and information:**A. Background of the Case**

1. It is my understanding that the Plaintiff in this action is Tarrant County, Texas.
2. It is my understanding that the Pharmacy Defendants in this action are as follows:
Kroger and Albertsons.

B. Opioid Prescribing/Dispensing

1. Opioid prescriptions in Tarrant County increased from 76 prescriptions per 100 persons in 2006 to a peak of 84.8 in 2012, higher than the national peak of 81.3 in 2012.¹⁸⁴⁸ Not reflected in this data set that starts in 2006, is the substantial increase in prescribing that occurred between the late 1990s and early 2010s in the US overall.¹⁸⁴⁹ Prescription dispensing rates for opioids have gradually decreased since their peak in 2012, but are still consistently higher in Tarrant County than in Texas or the United States overall.

Year	Opioid Dispensing Rate Per 100 Persons (U.S.) ¹⁸⁵⁰	Opioid Dispensing Rate Per 100 Persons (Texas) ¹⁸⁵¹	Opioid Dispensing Rate Per 100 Persons (Tarrant County) ¹⁸⁵²
2006	72.4	66.8	76.0
2007	75.9	71.2	78.9
2008	78.2	71.3	78.7
2009	79.5	71.8	79.9
2010	81.2	73.0	82.2
2011	80.9	72.0	81.6
2012	81.3	73.4	84.8
2013	78.1	70.0	80.7
2014	75.6	67.0	76.0
2015	70.6	59.8	68.8
2016	66.5	57.6	66.7
2017	59.0	52.2	60.0
2018	51.4	47.2	53.7

¹⁸⁴⁸ Centers for Disease Control and Prevention. U.S. County Opioid Dispensing Rates, 2006-2020.

¹⁸⁴⁹ See Report Section 3.

¹⁸⁵⁰ Centers for Disease Control and Prevention. U.S. Opioid Dispensing Rate Maps; Centers for Disease Control and Prevention. United States Dispensing Rate Maps (2019-2022). Last reviewed: December 11, 2023.

<https://www.cdc.gov/drugoverdose/rxrate-maps/index.html>.

¹⁸⁵¹ Centers for Disease Control and Prevention. U.S. State Opioid Dispensing Rates, 2006-2020; Centers for Disease Control and Prevention. State Opioid Dispensing Rates (2019-2022). Last Reviewed: October 31, 2023 <https://www.cdc.gov/drugoverdose/rxrate-maps/opioid.html>.

¹⁸⁵² Centers for Disease Control and Prevention. U.S. County Opioid Dispensing Rates, 2006-2020; Centers for Disease Control and Prevention. County Opioid Dispensing Rates (2019-2022). Last Reviewed: October 31, 2023 <https://www.cdc.gov/drugoverdose/rxrate-maps/opioid.html>

Year	Opioid Dispensing Rate Per 100 Persons (U.S.) ¹⁸⁵⁰	Opioid Dispensing Rate Per 100 Persons (Texas) ¹⁸⁵¹	Opioid Dispensing Rate Per 100 Persons (Tarrant County) ¹⁸⁵²
2019	46.8	42.3	50.6
2020	43.2	38.2	45.5
2021	42	36	43.9
2022	39.5	33.9	41.2

2. The Texas Department of State Health Services identified the following as the most commonly dispensed opioids in Texas in 2017: 1. Hydrocodone, 2. Tramadol, 2. Codeine, and 4. Oxycodone.¹⁸⁵³ Additionally, in Texas in 2017, the mean daily dosage of opioid dispensed per patient per day was 56.2 MME.¹⁸⁵⁴ More recent data from the Texas Prescription Monitoring Program show the mean daily dosage decreased further to 40.7 MME in 2019, 39.5 MME in 2020, 39 MME in 2021, and 38.6 MME in 2022.¹⁸⁵⁵

C. Transition to Heroin/Fentanyl

1. Opioid-related emergency department visits in Tarrant County have increased from 741 in 2018 to 954 in 2021,¹⁸⁵⁶ including 225 heroin related visits and 50 fentanyl related visits in 2021.¹⁸⁵⁷
2. As shown in the graph below, fentanyl deaths in Tarrant County have substantially increased in the past few years from 13 in 2019 to 172 in 2022 (preliminary data).¹⁸⁵⁸ There were 122 deaths reported for 2023, however these data are still “preliminary + partial.”¹⁸⁵⁹ Some of these fentanyl overdoses involved counterfeit prescription Percocet pills adulterated with fentanyl.¹⁸⁶⁰

¹⁸⁵³ Texas Department of State Health Services (2019). Texas Health Data: Texas Prescription Monitoring Program Data, 2019. URL: http://healthdata.dshs.texas.gov/TX_PMP

¹⁸⁵⁴ *Id.*

¹⁸⁵⁵ Texas Department of State Health Services. Texas Health Data. Texas Prescription Monitoring Program. Dispensing of Controlled Substances in Texas: Opioids. <https://healthdata.dshs.texas.gov/dashboard/drugs-and-alcohol/opioids/texas-prescription-monitoring-program>.

¹⁸⁵⁶ Texas Department of State Health Services. Texas Health Data: Opioid-Related Emergency Department Visits. <https://healthdata.dshs.texas.gov/dashboard/drugs-and-alcohol/opioids/opioid-related-emergency-department-visits>

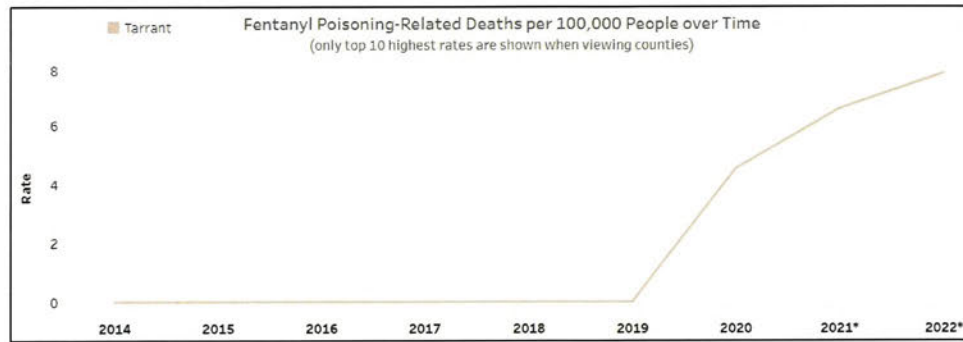
¹⁸⁵⁷ *Id.*

¹⁸⁵⁸ Texas Department of State Health Services. Texas Health Data: Fentanyl Trends.

<https://healthdata.dshs.texas.gov/dashboard/drugs-and-alcohol/fentanyl-trends>

¹⁸⁵⁹ *Id.*

¹⁸⁶⁰ Liou, T. (2023, November 20). Tarrant County district attorney creates new unit, focusing on narcotics cases, targeting drug dealers. CBS News Texas. <https://www.cbsnews.com/texas/news/tarrant-county-district-attorney-creates-new-unit-focusing-on-narcotics-cases/>

*Lembke Report**Confidential — Subject to Protective Order*

D. Conclusion

Tarrant County has been severely impacted by the opioid epidemic, which began with the misrepresentations of safety and efficacy of prescription opioids, combined with ubiquitous distribution and dispensing. As elsewhere, the epidemic of prescription opioids gave rise to the second and third waves of heroin and fentanyl epidemics, as the availability of prescription opioids decreased and their cost increased, relative to the greater availability and lower cost of heroin and illicit fentanyl. The ongoing epidemic of opioid addiction, dependence, and overdose death in the United States today can trace its origin directly to the oversupply of prescription opioids that began in the late 1990s.